Progesterone acutely increases LH pulse amplitude but does not acutely influence nocturnal LH pulse frequency slowing during the late follicular phase in women

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McCartney CR, Blank SK, Marshall JC. Progesterone acutely increases LH pulse amplitude but does not acutely influence nocturnal LH pulse frequency slowing during the late follicular phase in women. Am J Physiol Endocrinol Metab 292: E900–E906, 2007. First published November 22, 2006; doi:10.1152/ajpendo.00371.2006.—Progesterone (P) is the primary effector of LH (and by inference gonadotropin-releasing hormone) pulse frequency slowing in cycling women, but the time course of this action is unclear. We hypothesized that P administration to estradiol (E2)-pretreated women would slow LH pulse frequency within 12 h. We studied eight normally cycling women in two separate cycles (follicular phase, cycle days 7–11). After 3 days of E2 pretreatment (0.2 mg/day via transdermal patches), a 25-h blood sampling protocol (starting at 0800) was performed to define LH pulsatility. Oral micronized P (100 mg) or placebo (PBO) was administered at 1800 in a randomized, double-blind fashion, with treatment crossover occurring during a subsequent cycle. The 10-h mean P concentration increased from 0.6 ± 0.1 ng/ml before P (0800–1800) to 3.9 ± 0.3 ng/ml after P administration (2200–0800, P < 0.01). Ten-hour mean LH interpulse interval increased significantly after both P and PBO administration, with no significant difference between P and PBO. In contrast, mean LH, LH amplitude, and mean FSH increased significantly within 4 h of P administration, but not after PBO. We conclude that, in E2-pretreated women in the late follicular phase, 1) nocturnal LH pulse frequency is not acutely (within 12 h) influenced by P administration; 2) an acute increase in LH causes pronounced augmentation of gonadotropin pulse amplitude within 4 h; and 3) LH pulse frequency slows overnight during the second half of the follicular phase.

luteinizing hormone; gonadotropin-releasing hormone; follicle-stimulating hormone; estradiol; diurnal; circadian

PULSATILE GONADOTROPIN-RELEASING HORMONE (GnRH), secreted from a functionally integrated network of hypothalamic neurons called the GnRH pulse generator, stimulates LH and FSH synthesis and pulsatile secretion from pituitary gonadotropes. Variations in GnRH pulse frequency regulate LHβ and FSHβ transcription and mRNA expression (2, 4) and contribute to differential secretion of LH and FSH throughout the menstrual cycle (8, 11, 19, 39). Progesterone (P) appears to be the primary effector of GnRH pulse frequency slowing in adult women. LH (and by inference GnRH) pulse frequency slows coincidentally with P increases in the luteal phase, and administration of P to women during the follicular phase slows GnRH pulse frequency (34). Progesterone’s ability to slow GnRH pulse frequency appears to require the permissive presence of estradiol (E2) (7, 24, 33), probably reflecting the ability of E2 to induce hypothalamic P receptors (18, 27, 31, 32).

Some animal studies suggest that P suppression of GnRH pulse frequency occurs rapidly. For instance, in ovariectomized but E2-replete ewes, P dramatically suppresses GnRH pulse frequency over 12 h; this effect appears to begin within 2 h and is blocked by the P receptor antagonist mifepristone (RU-486) (33). Similarly, in bovine females, changes in LH pulse frequency are observed within 6 h of altered P concentrations (1).

In women, some hypothalamic-pituitary effects of P, such as increases of LH in E2-pretreated women, are observed within 12 h (3, 14, 23). However, the rapidity with which P slows GnRH pulse frequency in women remains unclear. During the follicular-luteal transition (periovulatory period) in women, P concentrations rise over several days (10), and LH pulse frequency slows during the early luteal phase after days of luteal P exposure (6, 26). P administration to women for 8 days (beginning in the early follicular phase) results in a 60% reduction in late follicular LH pulse frequency (34). More rapid reductions of LH frequency have not been demonstrated in cycling women during the follicular phase, although one study (22) suggested that raising plasma P to high levels (i.e., 20–28 ng/ml) slows LH pulse frequency by 45% within 12 h in postmenopausal, hypoestrogenic women.

We hypothesized that oral P administration after E2 pretreatment would result in a demonstrable suppression of GnRH pulse frequency within 12 h. Therefore, we evaluated the acute effects of oral P on LH pulse frequency in normally cycling adult women during the second half of the follicular phase (i.e., cycle days 7–11).

MATERIALS AND METHODS

Subjects. Eight healthy women (Table 1) with no evidence of hyperandrogenism were studied. All subjects reported regular and predictable menstrual cycles [every 28.4 ± 1.1 days (means ± SE)], and none exercised excessively. None of the women was obese (Table 1), and weight remained stable throughout the study. Reported race was white for all participants, with only one being of Hispanic ethnicity. None of the subjects reported previous pregnancy. All participants had normal screening laboratory tests (see Study procedures). Study participants took no hormonal medications for ≥90 days prior to study, and none was taking medications known to affect the reproductive axis. Only one subject reported previous use of oral contraceptives.

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Characteristics of study participants

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BMI, body mass index.

Study procedures. Study procedures were approved by the Institutional Review Board at the University of Virginia. Informed consent was obtained from study participants. Each volunteer underwent a detailed history and physical exam. All subjects were screened for hormonal and health-related abnormalities with determinations of LH, FSH, P, E₂, estrone, total testosterone (T), sex hormone-binding globulin, 17-hydroxyprogesterone, androstenedione, dehydroepiandrosterone sulfate, β-hCG, TSH, prolactin, complete blood count, chemistry and liver panels, fasting insulin, and fasting glucose.

Evidence of ovulation was obtained via a control cycle during which subjects had outpatient blood draws for plasma P ~9 and 6 days before their next anticipated menstrual bleed. A P level >3 ng/ml provided evidence for previous ovulation, and this evidence was required for subsequent General Clinical Research Center (GCRC) admission. During the subsequent menstrual cycle, transdermal E₂ patches [0.1 mg/day, 16 h patches, 2 patches (delivering a total of 0.2 mg/day) placed on the abdomen and changed every 2 days] were started on cycle days 4–8 and continued for a total of 4 days. Exogenous E₂ was given to standardize hypothalamic exposure to E₂ and to help ensure the presence of sufficient hypothalamic P receptors.

On days 7–11 of the study cycle, after exactly 3 days of E₂ administration, women were admitted to the GCRC for a 24-h sampling study. Subjects were admitted to the GCRC at 0600 (2 h prior to sampling), and a β-hCG and hematocrit were obtained to exclude pregnancy and anemia, respectively. Beginning at 0800, blood for later hormone measurement was obtained through an indwelling intravenous hepatic vein catheter over a 24-h period as follows: LH every 10 min; P every 30 min; FSH, E₂, and T every 2 h. After 10 h of sampling (i.e., at 1800), either oral micronized P (100 mg) suspension or oral placebo (PBO) suspension was administered in a randomized and double-blind fashion. E₂ administration was continued throughout the GCRC admission, but patches were removed at the completion of sampling. Volunteers were discharged on oral iron supplementation (325 mg twice daily) to help replenish iron stores.

The study followed a crossover design, with assessment of the acute effects of P and PBO (individually) on GnRH pulse frequency for each subject. Therefore, after the first GCRC admission, subjects again had outpatient blood draws for plasma P ~9 and 6 days before their next anticipated menstrual bleed. A P concentation >3 ng/ml suggested that cyclic ovulation was not interrupted by the first GCRC study, and such evidence was required for subsequent GCRC admission. During the subsequent menstrual cycle, subjects were admitted for another GCRC study identical to the first (including pretreatment with E₂), except that oral P was exchanged for PBO or vice versa. Subjects were asked to continue oral iron supplementation for 30 days after the second GCRC admission.

Diet and exercise were not controlled during the experiment, nor were diet and exercise records obtained. Participants were weighed at each GCRC admission, and weight did not change between admissions. Standard meals were given at standard times during GCRC admissions.

For convenience, the admission during which P was administered is hereafter called the "P admit," and the admission during which PBO was administered is called the "PBO admit."

Hormonal measurements. Hormone concentrations were measured in serum. Blood was withdrawn via an indwelling intravenous catheter into serum separator tubes and allowed to clot at room temperature prior to centrifugation. Serum was removed and stored at −20°C prior to analysis, which occurred within several days. Assays were performed by the Ligand Core Laboratory of the Center for Research in Reproduction at the University of Virginia Health System. All samples from an individual woman were analyzed in duplicate in the same assay for each hormone. The Cluster 7 pulse analysis program (see Data analysis below) utilizes both LH values for each time point; otherwise, the mean of the duplicates was used for data analysis. LH and FSH were measured by chemiluminescence [sensitivities 0.1 and 0.05 IU/l, intra-assay coefficients of variation (CVs) 2.3–4.1 and 2.2–2.6%, and interassay CVs 5.3–6.6 and 4.9–6.3%, respectively; Diagnostic Products, Los Angeles, CA]. Total T, E₂, and P were measured by radioimmunoassay (sensitivities 10 ng/dl, 10 pg/ml, and 0.1 ng/ml, respectively; intra-assay CVs 4.4–5.0, 5.2–6.8, and 4.5–5.4%, respectively; and interassay CVs 8.2–10.6, 11.8–15.8, and 6.7–7.3%, respectively; Diagnostic Products). Samples with measured values below assay sensitivity were assigned the value of the assay's sensitivity. To convert from conventional to Systeme International (SI) units: P × 3.18 (pmol/l); total T × 3.47 (pmol/l); E₂ × 3.671 (pmol/l).

Data analysis. LH pulses were identified using the computer algorithm Cluster 7 (37). The parameters used for analysis were a test nadir and peak size of 2 × 2 with a T statistic of 2.45 for both the upstroke and downstroke. Missing values represented <0.1% of the total and were ignored. If the amplitude of an LH pulse detected by the Cluster 7 program was less than the range of intra-assay variability for the LH chemiluminescence method, it was not considered a pulse in subsequent analysis, as previously described (21). Specifically, the following pulses detected by Cluster 7 were excluded from further analysis: pulses with a peak <1 IU/l and an amplitude <0.25 IU/l; pulses with a peak >1 and <5 IU/l with an amplitude <0.5 IU/l; and pulses with a peak >5 IU/l and an amplitude >1 IU/l.

The primary end point of our study was LH pulse frequency changes after P and PBO administration. We employed two methods of estimating LH pulse frequency within discrete time blocks. By the first method, we assessed average interpulse interval over a given time block. Pulse locations were assigned as the time point at which the LH increment first exceeded the increment required for assignment of a true pulse (see above). When an interpulse interval spanned the border of two time blocks, we assigned to the time block of interest only the proportion of the interpulse interval specifically occurring during that time block (see Fig. 1). Interpulse intervals occurring at the beginning or end of sampling were ignored unless they were known to be longer than the average interpulse interval for the time block; in this instance, a pulse was assumed to occur immediately before or after the beginning or end, respectively, of sampling (Fig. 1). By the second method of assigning LH pulse frequency, the number of pulses occurring within a given time block was divided by the number of hours in said time block, yielding an estimate of average pulses per hour (see Fig. 1). If a pulse occurred at the intersection between two time periods, the pulse was assigned to the preceding time period. Secondary end points included changes in mean LH and FSH concentrations, mean LH pulse amplitude, and mean sex steroid concentrations. LH pulse amplitudes were calculated as the peak LH concentration minus the preceding nadir concentration as determined by the Cluster 7 program.

LH pulse frequencies during two 10-h time blocks were compared: the 10-h time block immediately preceding P or PBO administration (i.e., 0800–1800, baseline) and the 10-h time block beginning 4 h after P or PBO administration (i.e., 2200–0800). To obtain a more detailed assessment of the timing of changes, we assessed LH pulse frequency in five 4-h time blocks: two 4-h time blocks immediately before and after the 10-h time block.
Wilcoxon signed-rank tests were used to examine changes (compared with baseline) in LH pulse frequency after administration of P or PBO. To determine whether observed changes were specifically attributable to P administration, we compared values observed after P administration to values expected under the null hypothesis (i.e., changes observed with PBO). The expected change after P under the null hypothesis was determined using the following formula: expected value after P = value before P × (value after PBO/value before PBO). For example, if an individual’s mean LH was 3 IU/l in the 10 h before PBO and 2 IU/l in the 10 h after PBO, and if mean LH was 4 IU/l in the 10 h before P administration, the expected mean LH in the 10 h after P administration (under the null hypothesis) would be 2.67 [i.e., 4 × (2/3)]. This calculation was performed for each individual, and Wilcoxon signed-rank tests were used to compare expected and observed changes after P administration. Any differences were assumed to reflect a specific effect of P administration. We used similar methods to evaluate changes over 4-h time blocks, with baseline values calculated as the average of the two 4-h time blocks immediately preceding P or PBO administration. We performed similar testing for mean LH and FSH, mean LH pulse amplitude, and mean sex steroid concentrations.

The study of 11 individuals was projected to provide 80% power to detect a 30% or greater reduction of LH pulse frequency specifically attributable to P. However, preliminary analysis of the data for eight subjects revealed no indication that P reduced LH frequency within 12 h. In fact, LH pulse frequency was reduced slightly more after PBO compared with P. For this reason, we felt it unnecessary to study three additional research volunteers.

RESULTS

Sex steroids. The 10-h mean P concentration increased from 0.6 ± 0.1 ng/ml before P to 3.9 ± 0.3 ng/ml after P administration (P < 0.01). As shown in Fig. 2, plasma P levels peaked quickly, reaching values of 7.5 ± 1.2 ng/ml during the first 4 h after administration, falling thereafter to 4.3 ± 0.4 and 3.7 ± 0.3 ng/ml (4–8 h and 8–12 h, respectively, after P administration). No change in P concentration was observed after PBO administration (0.7 ± 0.1 ng/ml before and 0.6 ± 0.1 ng/ml after PBO). Mean E2 values were 214 ± 46 pg/ml during the P admit and 169 ± 23 pg/ml during the PBO admit [P = not significant (NS)]. Mean T levels were 28.5 ± 5.6 and 29.2 ± 4.1 ng/dl during P and PBO admits, respectively (P = NS; Fig.

Fig. 2. Sex steroid concentrations. Mean ± SE steroid values from placebo (PBO) admit (□) and progesterone (P) admit (■) are shown. Arrows denote the timing of PBO or P administration. Conversion from conventional to Systeme International (SI) units: P × 3.18 (nmol/l); total testosterone (T) × 0.0347 (nmol/l); estradiol (E2) × 3.67 (pmol/l).
2). There were no significant differences in E2 or T across 10-h time blocks during either admission.

**LH pulse frequency, mean LH, and LH pulse amplitude.** A representative subject’s LH (and P) concentration-time series are shown in Fig. 3. A (PBO admit) and B (P admit). LH pulse characteristics over 10-h time blocks are shown in Fig. 4A. Mean LH interpulse interval increased from 86 ± 4 min before P to 103 ± 10 min after P administration (P < 0.05). Similarly, mean LH interpulse interval increased from 78 ± 4 min before PBO to 100 ± 8 min after PBO administration (P < 0.05). When normalized for changes after PBO, there were no changes in LH interpulse interval attributable to P administration. When assessing LH pulse frequency via number of LH pulses per hour, changes after P and PBO were not statistically significant compared with baseline (P = 0.08 and 0.06, respectively) or compared with each other. In contrast to LH pulse frequency, P effected significant changes in 10-h mean LH and LH amplitude, which increased 3.2- and 5.1-fold, respectively, after P administration (P < 0.01 vs. baseline). No change in mean LH or LH amplitude was observed after PBO, and changes after P were specifically attributable to P administration (P < 0.01).

**Fig. 3.** Representative examples of LH and P concentration time series in a single subject. A: PBO admit. B: P admit. LH and P data points are shown as ■ and □, respectively. *Detected LH pulses. Arrows denote the timing of PBO or P administration. Conversion from conventional to SI units: P × 3.18 (nmol/l).

**Fig. 4.** LH pulse characteristics over 10-h (A) and 4-h (B) time blocks. Data points for the PBO and P admissions are shown as □ and ■, respectively. P and PBO are given at 1800. **P < 0.01 change after P vs. change after PBO; *P < 0.05 vs. baseline; bP < 0.01 vs. baseline.
acutely affects LH secretion, inasmuch as LH interpulse interval increased (P < 0.05) and LH pulses per hour decreased (P < 0.05) by the last 4-h time block after PBO. Although LH pulse frequency slowed after P, this did not reach statistical significance. The changes in 4-h LH interpulse interval and LH pulse count after P administration were not significantly different compared with changes after PBO. Mean LH and LH amplitude was markedly increased compared with baseline in all 4-h time blocks after P administration (P < 0.05 for mean LH during the first 4 h vs. baseline and P < 0.01 for all other comparisons). Whereas mean LH amplitude did not change after PBO administration, mean LH concentrations were lower than baseline during the first two 4-h time blocks after PBO administration (P < 0.01). Changes in mean LH and LH amplitude after P were significantly different compared with changes after PBO (P < 0.01).

**Mean FSH.** Ten-hour mean FSH increased from 3.6 ± 0.5 IU/l before P to 6.9 ± 1.2 IU/l after P administration (P < 0.01; Fig. 5A). However, no significant change was observed with PBO. When normalized for changes observed after PBO, there was a significant increase in mean FSH attributable to P administration (P < 0.01). For each 4-h time block after P administration (Fig. 5B), mean FSH was higher than baseline (P < 0.05 for the first 4 h and P < 0.01 thereafter). No significant changes in FSH occurred after PBO, and changes observed after P were specifically attributable to P administration (P < 0.05 for the first 4 h and P < 0.01 thereafter).

**DISCUSSION**

The present experiment, in which a single dose of oral P was administered to women pretreated with E2 during the latter half of the follicular phase, disclosed three primary findings of interest: 1) acute P administration did not alter nocturnal LH pulse frequency within 12 h; 2) acute P administration caused a rapid (within 4 h) and pronounced increase in gonadotropin secretion; and 3) LH pulse frequency exhibited diurnal changes (nocturnal slowing) during the second half of the follicular phase.

Of primary interest, the results of this study indicate that increases of P concentrations in the evening to low to mid-luteal levels do not slow nocturnal LH (and by inference GnRH) pulse frequency within 12 h in adult women. Although LH pulse frequency indeed decreased shortly after P administration, similar decreases were observed shortly after PBO administration. This finding suggests that LH pulse frequency exhibits nocturnal slowing during the second half of the follicular phase but that P administration does not acutely alter this pattern. Whereas late follicular (cycle days 9–12) LH pulse frequency is reduced by 60% when P is given for the preceding 8 days (34), this reduction of LH frequency appears to require >12 h of P exposure. The absence of P-induced LH pulse frequency slowing in our study contrasts with a study of postmenopausal women that suggested LH pulse frequency slowing by 45% within 12 h of intramuscular P (50 mg) administration (22). However, the women in these two studies had dissimilar sex steroid milieu (e.g., postmenopausal vs. preovulatory E2 levels; reduced ovarian T after menopause). Additional methodological differences include the absence or presence of a control state (i.e., evaluation after PBO administration), different LH sampling frequencies (every 15 min vs. every 10 min), different LH assays, different methods of pulse detection (pulses defined by LH increments vs. application of the Cluster 7 computerized pulse detection algorithm), and different timing of P administration (0600 vs. 1800).

It is unclear whether E2 pretreatment modified the actions of P on LH pulsatility, and endogenous follicular E2 levels may have been sufficient to allow acute P actions. It also remains unknown whether acute rises in P might differently affect LH pulse frequency in states of increased negative feedback sensitivity to sex steroids [e.g., early puberty (12)] or states of decreased negative feedback sensitivity to sex steroids [e.g., hyperandrogenic states such as polycystic ovary syndrome (5, 25)]. Further study is required to explore these questions.

Nocturnal, sleep-related slowing of LH pulse frequency during the early follicular phase is well described (6, 9, 20, 28–30, 35). However, the data regarding nocturnal LH frequency slowing in the late follicular phase are less robust. Although several studies by Loucks and colleagues (15–17) suggest that late follicular LH pulse frequency slows by 20–30% during sleep, others have not found nocturnal decreases in LH frequency during the late follicular phase (6, 28, 29, 35). The reasons for discrepancies among these studies are unclear, but possibilities include the use of different LH assays, unfavorable LH sampling frequencies [e.g., every 15 (28, 29) or 20 (35) min vs. every 10 min (15–17)], and older methods of pulse detection [e.g., Santen and Bardin method (6, 35)]. Methods for assigning LH pulse frequency differed as well, although employed methods were not always clearly reported. Moreover, some methods of assessing LH pulse changes may have masked true differences. For instance, although one study described significant diurnal changes of LH pulse frequency in 11 of 14 women in the late follicular phase, cosinor analysis of composite data revealed no significant changes (28).

In addition to the above, some (6, 28, 36) but not all (35) studies have suggested diurnal slowing of LH pulse frequency during the luteal phase. Taken together, these and our findings suggest that diurnal slowing of LH pulse frequency may occur throughout the menstrual cycle in adult women, with changes being most prominent in the early follicular phase. The physiological relevance of diurnal changes of LH pulsatility in adult women remains unknown, but it is of interest that nighttime work can be associated with disruption of menstrual cyclicity (9). Since GnRH pulse frequency contributes to the differential control of LH and FSH synthesis and secretion, Hall et al. (9)
have recently suggested the possibility that disruption of diurnal GnRH pulse frequency variation may lead to abnormal secretion of LH and FSH with resultant menstrual disturbances.

Nocturnal slowing of LH frequency in the early follicular phase appears to be specifically related to sleep, with LH pulses being uncommon during rapid-eye-movement and slow-wave sleep but more common following brief awakenings (9); this effect may be mediated by hypothalamic opioids (30). Formal assessment of sleep was not performed in our study, and although precautions against waking sleeping subjects were taken, it remains possible that frequent blood sampling disturbed normal sleep patterns in our study (38). Regardless, by analogy to observations in the early follicular phase (9), any such sleep disturbances might be expected to limit overnight slowing of LH pulse frequency. For this reason, we may have underestimated the nocturnal slowing of LH pulse frequency occurring in the latter half of the follicular phase.

This experiment disclosed a rapid (within 4 h) and pronounced augmentation of gonadotropin secretion after oral P administration. Similar findings have been observed with P administration after E2 priming in women (3, 14, 23); these studies suggest gonadotropin effects within 12 h, but the rapidity with which P augments LH release in vivo has been otherwise unclear. For instance, one study demonstrated that P injections (sufficient to raise plasma P from 0.3 to 0.9 ng/ml) in E2-pretreated women resulted in a significant gonadotropin increase (e.g., 6- to 7-fold increase in LH concentration) within 12 h, with the earliest measurement after P injection (3). A study of E2-pretreated women with hypogonadotropic hypogonadism receiving exogenous pulsatile GnRH also showed an increase in LH within 12 h of P administration, which raised P levels to ~1 ng/ml (23). Perhaps the most detailed study in this regard was one investigating the roles of E2 and P in midcycle surge initiation (14). Therein, P infusion (raising P from 0.4 to 1.2 ng/ml over 4 h, with a slower increase thereafter) in E2-pretreated women was followed in 11 h (when P was 1.7 ng/ml) by a marked increase in LH and FSH, and similar intervention had more rapid actions on plasma gonadotropins (increased within 5–6 h) in postmenopausal but E2-replete women (14). These findings in cycling women suggest a longer latency period than that observed in our study; alternatively, this finding may reflect a threshold P concentration, achieved rapidly in our study, required for gonadotropin augmentation.

The acute effects of P on gonadotropin secretion appear to be related, at least in part, to augmentation of GnRH-stimulated release of gonadotropins from pituitary gonadotropes (13, 23). On the basis of these data, it is generally held that the late follicular rise in P, which begins ~12 h before the LH surge (10, 14), is an important mechanism contributing to the midcycle LH surge.

In conclusion, our experiment has disclosed two previously undescribed physiological findings: 1) LH pulse frequency is not acutely (within 12 h) influenced by P administration sufficient to acutely raise plasma P to low to mid-luteal levels, and 2) acute increases in P rapidly (within 4 h) result in marked augmentation of gonadotropin secretion. In addition, this study corroborates earlier studies suggesting that LH pulse frequency slows overnight during the second half of the follicular phase. It remains unclear whether a similar study paradigm would differ affectively affect LH pulsatility in the setting of different steroid hormone milieu or in states of either increased or decreased negative feedback sensitivity to sex steroids.

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REFERENCES


