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Sex Differences in Acute Luteinizing Hormone Responses to Gonadectomy Remain after Progesterone Antagonist and Dopamine Agonist Treatment[1]

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ABSTRACT

In male rats, LH pulse frequency and amplitude increase dramatically by 24 h after gonadectomy; in females they increase only slightly by this time. Mean FSH levels increase significantly in both sexes by 24 h after gonadectomy. The objectives of the present studies were to compare pulsatile LH, FSH, and prolactin (PRL) secretion in intact versus gonadectomized and in male versus female rats, and to determine whether the acute postovariectomy lag in LH rise is due to a lingering effect of the higher PRL and/or progesterone (P) levels seen in intact females. LH pulse amplitude, frequency, and mean levels increased significantly by 24 h after gonadectomy in both sexes, but the increases were greater in the males. FSH mean levels, but not pulse amplitude or frequency, increased similarly in both sexes by 24 h after gonadectomy. PRL did not change with gonadectomy. Treatment with CB-154 (a dopamine agonist), with or without RU486 (a P antagonist), 1 h before gonadectomy significantly suppressed pulsatile PRL secretion 1 day later in both sexes. There was no effect of either treatment on LH secretion. We have demonstrated that there is a sex difference in LH, but not FSH or PRL, pulsatility at 24 h after gonadectomy, and that female rats' higher PRL and P levels do not account for their slow rate of LH rise after ovariectomy.

INTRODUCTION

Serum LH pulse frequency and amplitude increase significantly by 24 h after gonadectomy in both male [1] and female [2] rats; however, the rate of increase is much more rapid in males than in females. LH pulse frequency and amplitude in male rats respond to the removal of negative feedback with 3-fold increases by 24 h after castration [1], whereas in females they increase by only 1.5- to 2-fold [3], if at all [4], by this time after ovariectomy. Serum FSH, in contrast to LH, rises at the same rate after gonadectomy in both sexes [5].

Prolactin (PRL) in intact male and female rats is secreted in irregularly spaced pulses [6, 7]. Mean PRL levels in males [6] are similar to the mean PRL levels seen in females [7, 8] on the mornings of metestrus and diestrus, are lower than the mean levels seen in females [7] on the afternoon of diestrus by up to an order of magnitude and are lower than the surge levels seen on the afternoon of proestrus by two orders of magnitude [7, 8]. In the male, there is no postcastration change in pulsatile PRL secretion [6]. Pre- and postovariectomy pulsatile PRL secretion have not been compared in a single study, but there appears to be no difference between the pulsatile PRL secretion on diestrus [7] and 2 wk after ovariectomy, when pulses occur at a frequency of slightly less than one per hour with an amplitude of about 7 ng RP-3/ml [9]. There is considerable evidence that high PRL levels can prevent or suppress the acute postgonadectomy rise in serum LH in both female [10, 11] and male [12, 13] rats. Other studies have shown that hypoprolactinemia enhances gonadotropin release [14, 15]. We hypothesized that the higher average levels of PRL in intact females compared to levels in intact males may account for the delayed LH rise after ovariectomy.

Like PRL, the progesterone (P) levels of 10–50 ng/ml [16, 17] found in intact females are higher than those in intact males, in which P levels are negligible (2–6 ng/ml), except after exposure to a stressor [18]. We hypothesized that the initially higher levels of P in female rats could also be responsible for their delayed LH rise after ovariectomy. Diestrous levels of P replacement given at the time of ovariectomy on metestrus cause LH pulse amplitude to be suppressed 24 h later [3] and mean LH levels [16] to be suppressed 4 days later compared to untreated ovariectomized rats.

The aims of the following studies, then, were to compare pulsatile LH, FSH, and PRL secretion in intact versus gonadectomized rats and in male versus female rats in the same study; and to determine whether, given the higher levels of P and PRL in intact female than in male rats, the acute postovariectomy lag in the rate of LH rise is partially caused by continued occupancy by P and/or PRL of their receptors. To prevent continued receptor occupancy, a P receptor antagonist (RU486) or a PRL secretion suppressor (CB-154) was used.

MATERIALS AND METHODS

Animals

Female and male Sprague-Dawley CD rats (Charles River, Portage, MI) were obtained at 60 days of age, housed 3 or

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4 per cage, and maintained in controlled temperature (20°C) and lighting conditions (14L : 10D; lights-on, 0500 h) with water and food provided ad libitum. No rats were used until at least 1 wk after arrival, and females were used only after they had shown at least two 4-day estrous cycles by daily monitoring of vaginal cytology.

Surgery and Blood Collection

All bilateral gonadectomies occurred at 0900 h. Between 0900 and 1100 h the animals were fitted with right atrial cannulae via the external jugular vein. Cannulae consisted of Silastic tubing (0.635 mm i.d. × 1.193 mm o.d.; Dow Corning, Midland, MI), 2.7–3.3 cm in length, which was connected to polyethylene (PE-50, Clay Adams, Parsippany, NJ) tubing at the point of entry into the blood vessel. The tubing was tunneled under the skin and exteriorized at the nape of the neck. All surgery in experiment I was performed under methoxyflurane anesthesia, while ketamine hydrochloride-xylazine anesthesia (Ketaset, Aveco Co., Fort Dodge, IN, and Rompun, Mobay Corp., Shawnee, KS) was used for experiment II.

Each animal was serially bled at 6-min intervals from 0900 to 1200 h 1 day after cannulation: 0.5 ml blood was withdrawn per sample, and after every second sample, 1 ml of blood replacement mixture [19] consisting of saline-washed donor red blood cells reconstituted with Plasmanate human plasma protein (Cutter Biological, Berkeley, CA) was administered. After each sample was drawn, the cannula was flushed with heparinized saline (20 IU/ml). Samples were allowed to clot overnight and then were centrifuged; plasma was stored at −70°C until subsequent RIA. In experiment I, LH and PRL levels were measured in every sample; FSH was measured in samples 3–29; P was measured in samples 1, 2, and 30. Since no sex difference was observed in FSH secretion at 24 h after gonadectomy, only LH, PRL, and P were measured in experiment II.

Drugs

The dopamine (DA) agonist bromocriptine mesylate, CB-154 (Sandoz Pharmaceuticals, East Hanover, NJ) was used to suppress PRL. Unlike the naturally occurring ergot alkaloids, this semisynthetic compound has low pressor activity [20]. CB-154 has been shown to act directly on the pituitary to inhibit PRL release in vitro [15, 21]. The P receptor antagonist RU486 (Roussel-UCLAF, Paris, France) was used to suppress P. This compound has a higher affinity for the P receptor than does P itself [22].

RIA

Plasma LH was measured using an ovine : rat system in experiment I (NIH LH S25 as standard and anti-rat LH antibody S-10 from the NIDDK kit [NIDDK, Baltimore, MD]; results are expressed as NIH LH S25 standard) and a rat : rat system from NIDDK in experiment II (rLH-RP-2 as standard and anti-rat LH antibody S-10; results are expressed as RP-2). The S25 and RP-2 standards are equivalent. The NIDDK rat : rat system was used to measure plasma FSH (rFSH RP-2 as standard and anti-rat FSH antibody S-11). The NIDDK rat : rat system was also used for PRL (rPRL RP-3 as standard and anti-rat PRL antibody S-10; results are expressed as RP-3 standard). Plasma P levels were measured using a commercially available kit (ICN Biomedicals, Carson, CA). Mean intraassay coefficients of variation (CV) were 9% for LH, 11% for FSH, and 5% for PRL in experiment I. The sensitivities of the assays at 80% binding were 0.04 ng/tube for LH, 0.22 ng/tube for FSH, and 0.09 ng/tube for PRL. Because of the large number of samples, two LH and PRL assays each were run for experiment II: the intraassay CVs were 24% and 8% for LH and 14% and 7% for PRL. The sensitivities of the assays were 0.06 and 0.03 ng/tube at 80% and 90% binding, respectively, for LH, and 0.08 and 0.07 ng/tube at 80% and 90% binding, respectively, for PRL. The interassay CVs for all assays for both experiments were 24% for LH and 44% for PRL. For P, a single assay was run for both experiments: the intraassay CV was 10%, and the sensitivity was 0.64 ng/tube at 80% binding. Most of the samples were run using 50 μl of plasma; however, the LH samples from castrated rats were also run at 25 μl.

Data Analysis

The ULTRA pulse detection program [23] was used to determine significant LH and PRL pulses. This program takes as input the series of data values, the CVs of the concentration ranges of the assay, and a threshold expressed in terms of number of assay CVs. The program proceeds by eliminating all increments and decrements from the series that do not exceed the specified number of local intraassay Cvs. For these analyses, a two-CV threshold was utilized. Data from each assay were subjected to the ULTRA analysis using CVs only from that assay. Mean pulse amplitude and frequency values from the ULTRA analysis, as well as the mean of the serial samples from each animal, were analyzed by two-way ANOVA, with sex and treatment as between variables, using the CRUNCH interactive statistical package (Crunch Software, Oakland, CA), and are expressed as mean ± SE.

Experiment I: Control Male and Female LH, FSH, PRL, and P Levels

Male and female rats were divided into two treatment groups. At 0900 h, 4 metestrous females and 4 males were bilaterally gonadectomized and fitted with atrial cannulae. The intact male and estrous female controls were left gonadally intact and were also cannulated at 0900 h. In an effort to minimize stress during the blood sampling procedure, the animals were moved to the isolated sampling room immediately after surgery and were left there over-

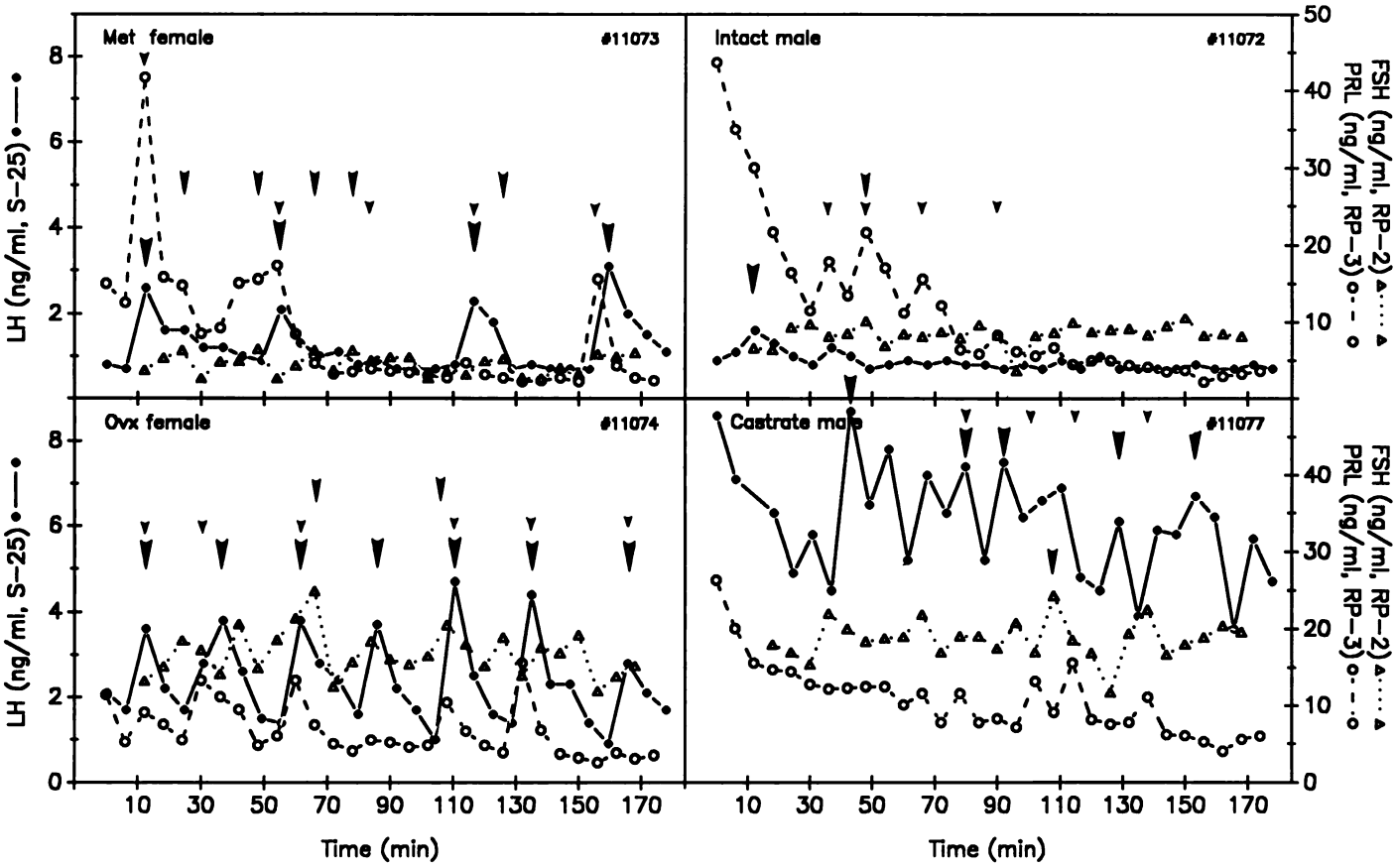

FIG. 1. Typical pulsatile plasma LH (closed circles), FSH (open triangles), and PRL (open circles) release profiles from intact (top) and 24 h postgonadectomy (bottom) male (right) and female (left) rats. Samples were taken from 0900 to 1200 h at 6-min intervals. Large, medium, and small arrowheads point to significant LH, FSH, and PRL pulses, respectively, as determined by ULTRA [23].

night. Blood samples were taken every 6 min between 0900 and 1200 h on the day after surgery.

Experiment II: CB-154 and RU486 Treatment at the Time of Gonadectomy

Sixteen metestrous females and 16 males were divided into four treatment groups. At 0800 h, the animals received injections of one of the following: (1) 6 mg of RU486/kg body weight/ml corn oil, (2) 0.5 mg of CB-154 in 0.5 ml oil, (3) both drugs, or (4) 0.5 ml oil vehicle. One hour later, all animals were gonadectomized and cannulated. Serial sampling occurred from 0900 to 1200 h on the day after surgery. The dose of RU486 used had been shown in preliminary studies in our laboratory to be the lowest dose capable of blocking the LH and FSH preovulatory surges when administered at 1200 h on proestrus. The dose of CB-154 was chosen because preliminary trials in our laboratory and the work of other researchers [24] had demonstrated that this dose suppressed PRL to undetectable levels in male and female rats.

RESULTS

Experiment I: Control Male and Female LH, FSH, PRL, and P Levels

Representative LH, FSH, and PRL profiles from one animal in each group are shown in Figure 1. As expected, LH and FSH increased by 24 h after gonadectomy in rats of both sexes; however, the LH rise in the females was smaller than in the males. There were already significant sex differences in LH secretion before gonadectomy. Males had lower mean LH (not significant), lower LH pulse amplitude ($p < 0.02$ by one-way ANOVA), and lower pulse frequency ($p < 0.001$ by one-way ANOVA) than did metestrous females (Fig. 2). As expected, the males had a much greater postgonadectomy LH rise (Fig. 2). Although LH mean levels, pulse amplitude, and pulse frequency all increased significantly after gonadectomy in both sexes ($p < 0.001$, effect of surgery by two-way ANOVA), the mean LH levels in the males were significantly higher than in the females ($p < 0.003$, interaction between sex and surgery by two-way ANOVA). This sex difference was mainly attributable to higher interpulse nadirs in the males since there were no signif-

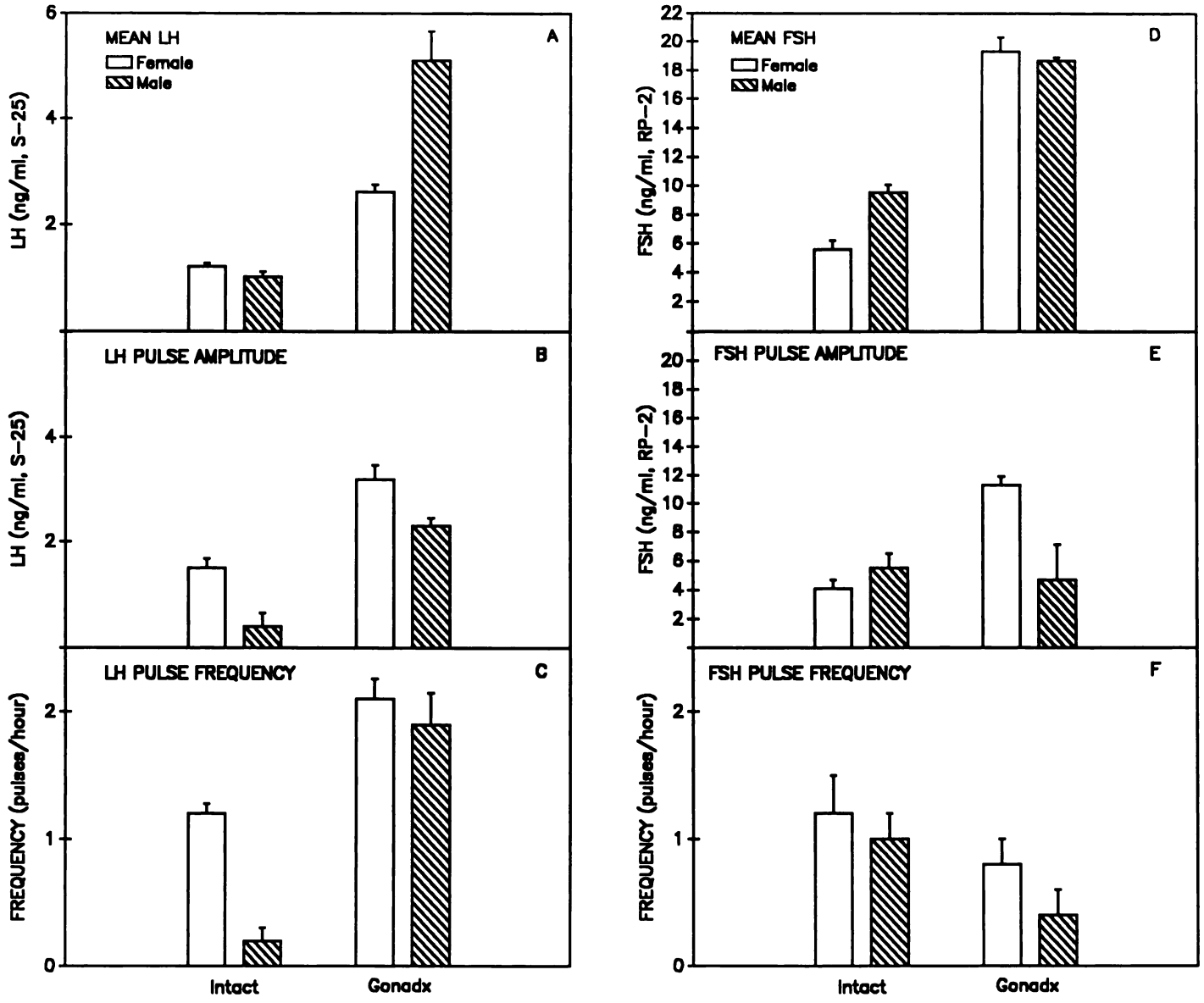

FIG. 2. Summary of pulsatile LH and FSH release during 3-h serial blood sampling of metestrous females, intact males, and females and males 24 h after gonadectomy, as indicated on the graph (n = 4 per group). A and D: Mean ± S.E. hormone levels for each treatment group. B and E: Mean ± S.E. of pulse amplitudes. C and F: Mean ± S.E. of pulse frequencies. There was a significant increase in LH mean levels, pulse amplitude, and pulse frequency in the gonadectomized versus intact animals ($p < 0.001$). The mean LH levels in the castrated males were significantly higher than in the ovariectomized females ($p < 0.003$). The percentages of increase in pulse amplitude ($p < 0.001$) and pulse frequency ($p < 0.02$) over intact levels were significantly higher for the males than the females. The mean FSH levels were also significantly higher ($p < 0.001$) in the 24-h gonadectomized than in the intact animals. FSH pulse amplitude was significantly higher in the ovariectomized than in the intact females (interaction between sex and surgery: $p < 0.006$).

icant differences in LH pulse amplitude or frequency between males and females at 24 h after gonadectomy. Mean LH levels (Fig. 2A) and LH pulse amplitude (Fig. 2B) in the males increased 5-fold versus 2-fold in the females, and LH pulse frequency increased 20-fold in the males versus less than 2-fold in the females (Fig. 2C). Mean FSH levels were greater in intact males than in metestrous females, but by 24 h after gonadectomy FSH levels in the males had doubled while those of the females had tripled to nearly identical levels (Fig. 2D). FSH pulse frequency was not significantly different in the gonadectomized animals compared to the intact animals of both sexes (Fig. 2F). FSH pulse amplitude was also unchanged after orchidectomy, but there was a significant increase in pulse amplitude in the ovariectomized females compared to the metestrous females ($p < 0.02$, Fig. 2E); however, the postgonadectomy rise in mean FSH levels in both sexes can be attributed to a greatly increased interpulse nadir (Fig. 1).

Despite our precautions to avoid stress, mean PRL levels during the first hour were significantly ($p < 0.001$) higher

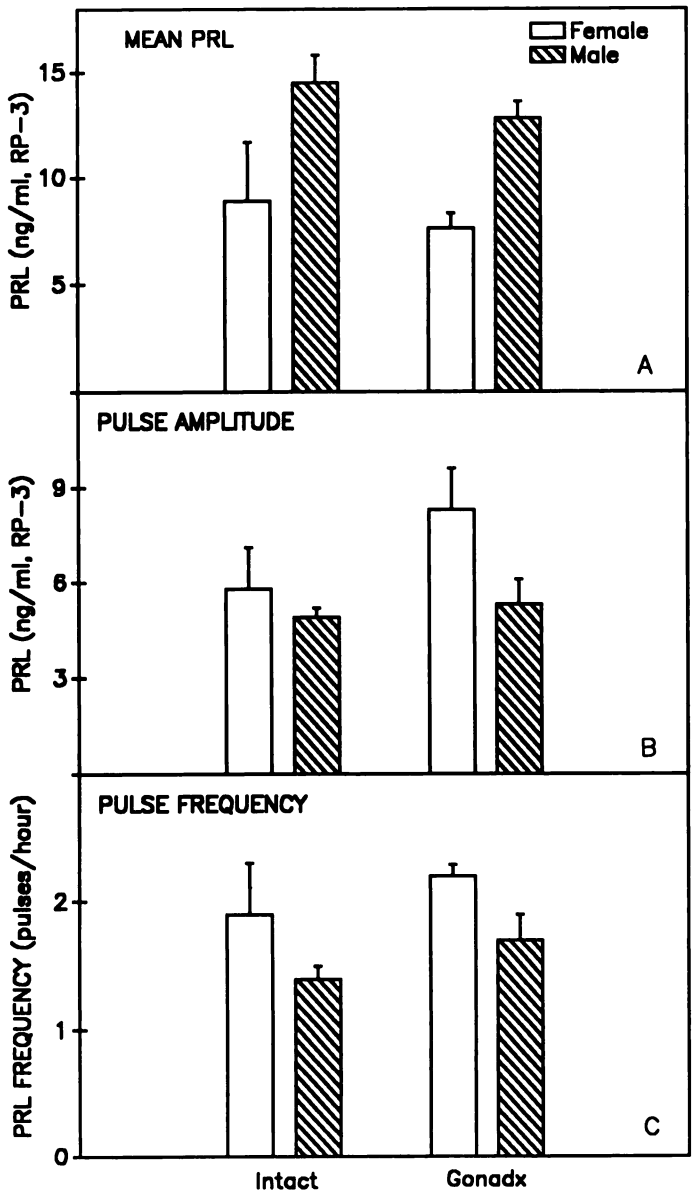

FIG. 3. Summary of pulsatile PRL release during 3-h serial blood sampling of metestrous females, intact males, and females and males at 24 h after gonadectomy, as indicated on the graph (n = 4 per group). A: Mean ± SE PRL levels. B: Mean ± SE of pulse amplitudes. C: Mean ± SE of pulse frequencies. There were no significant differences among groups.

than during the second and third hours of sampling, and during the second hour PRL levels were still significantly higher than during the third hour ($p < 0.008$). Mean PRL levels were higher ($p < 0.007$) in intact males versus intact females and in castrated males versus ovariectomized females during the first 2 h of blood sampling (Fig. 1); as a result the mean PRL levels for the entire bleeding period were slightly greater in males than in females (Fig. 3; not significant). During the third hour of blood sampling there were no significant differences in mean PRL levels among the four experimental groups. Levels were 5.1 ± 1.1 ng/ml in intact males, 3.9 ± 0.3 ng/ml in metestrous females, 6.3 ± 0.5 ng/ml in castrated males, and 5.4 ± 0.5 ng/ml in ovariectomized females. Similarly, P levels were also significantly higher at the beginning of serial blood sampling than at the end across all groups ($p < 0.03$; data not shown). The intact females had the highest mean P levels, 16.6 ± 2.5 ng/ml; the values in the other three groups ranged from 2.0 ng/ml (assay limit of sensitivity) to 4.6 ng/ml. There were no significant effects of sex or surgery on PRL pulse amplitude, pulse frequency, or mean levels (Fig. 3).

Experiment II: CB-154 and RU486 Treatment at the Time of Gonadectomy

As in experiment I, secretion of both LH and PRL was clearly pulsatile in the controls, and the RU486-treated groups also had pulsatile release of both hormones. Significant sex differences in LH secretion again were observed 24 h after gonadectomy. Pulse frequency ($p < 0.007$), pulse amplitude ($p < 0.002$), and mean levels ($p < 0.001$) of LH (Fig. 4) were all significantly higher in males than in females. There was no significant effect of RU486 and/or CB-154 treatment on LH secretion in either sex (Fig. 4), nor was there any effect of drug treatment on P levels (data not shown).

As in the first experiment, the mean PRL levels during the first hour of blood sampling were higher than during the second and third hours in both oil- and RU486-treated animals ($p < 0.001$). There was a significant sex difference in that the males had more elevated PRL during the first hour than did the females ($p < 0.02$). There were no significant differences in mean PRL levels among the oil- and RU486-treated groups during the third hour. PRL levels were 6.8 ± 0.8 ng/ml in the oil-treated females, 4.7 ± 1.6 ng/ml in the oil-treated males, 6.2 ± 1.6 ng/ml in the RU486-treated females, and 5.4 ± 2.0 ng/ml in the RU486-treated males. The PRL pulse amplitude across all groups of female rats in this experiment was significantly higher ($p < 0.002$) than that of males (Fig. 5B). Treatment with CB-154, with or without RU486, significantly suppressed PRL pulse frequency ($p < 0.001$), amplitude ($p < 0.002$), and mean levels ($p < 0.001$) in both sexes; RU486 had no effect on PRL (Fig. 5). There was no effect of any of the drug treatments on P levels (data not shown). Unexpectedly, P levels were higher at the end than at the beginning of blood sampling across all groups ($p < 0.02$), exactly the opposite of the result in experiment I and with PRL.

DISCUSSION

Our data corroborate previous reports characterizing pulsatile LH release at 24 h after gonadectomy [1–3], with males manifesting a dramatic increase over intact levels and females showing slighter rises. To our knowledge this is the first time that male and female pulsatile LH, FSH, and PRL release after gonadectomy has been examined in a sin-

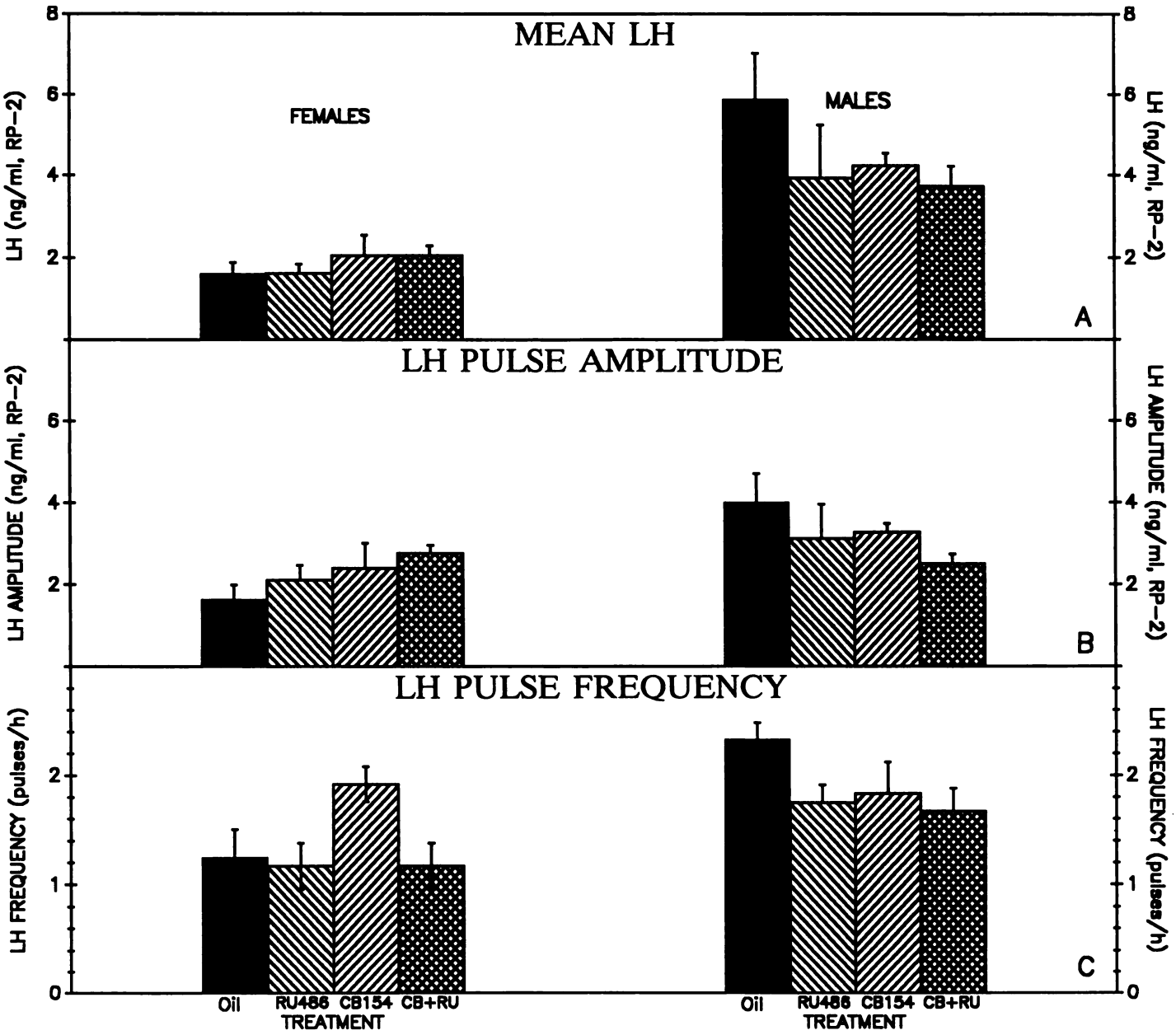

FIG. 4. Summary of pulsatile LH release during the 3-h serial blood sampling of females (left) and males (right) 24 h after gonadectomy. Treatment groups are indicated along the X axis (oil, RU486, CB-154, CB-154 plus RU486; n = 4 per group). A: Mean ± SE LH levels for each treatment group. B: Mean ± SE of pulse amplitudes. C: Mean ± SE of pulse frequencies. Mean levels ($p < 0.001$), pulse amplitude ($p < 0.002$), and pulse frequency ($p < 0.007$) were all higher in the males than in the females. There were no significant effects of CB-154 or RU486 treatment on LH secretion.

gle study. At 24 h after gonadectomy, pulse amplitude, frequency, and mean levels of LH and mean levels of FSH were significantly greater than in intact animals for both sexes. At this time after gonadectomy, the mean LH levels in the males were significantly higher than those of the females, whereas mean FSH levels did not differ between the sexes. Moreover, the postgonadectomy rise in mean FSH levels was not due primarily to increases in FSH pulse amplitude or frequency, but rather to rising interpulse nadirs. In both females and males, increases in LH pulse amplitude and frequency clearly contributed to the elevated mean LH levels after gonadectomy; however, in males, rising interpulse nadirs were also evident.

The rise in FSH levels after ovariectomy is likely due to the combined effects of inhibin and estradiol (E) withdrawal. Inhibin is capable of suppressing FSH to intact levels only in acutely ovariectomized females [25]. At later times after ovariectomy, only superimposed inhibin plus E is capable of suppressing FSH to intact levels [26]. In contrast, in the male rat, the postcastration rise in FSH can be com-

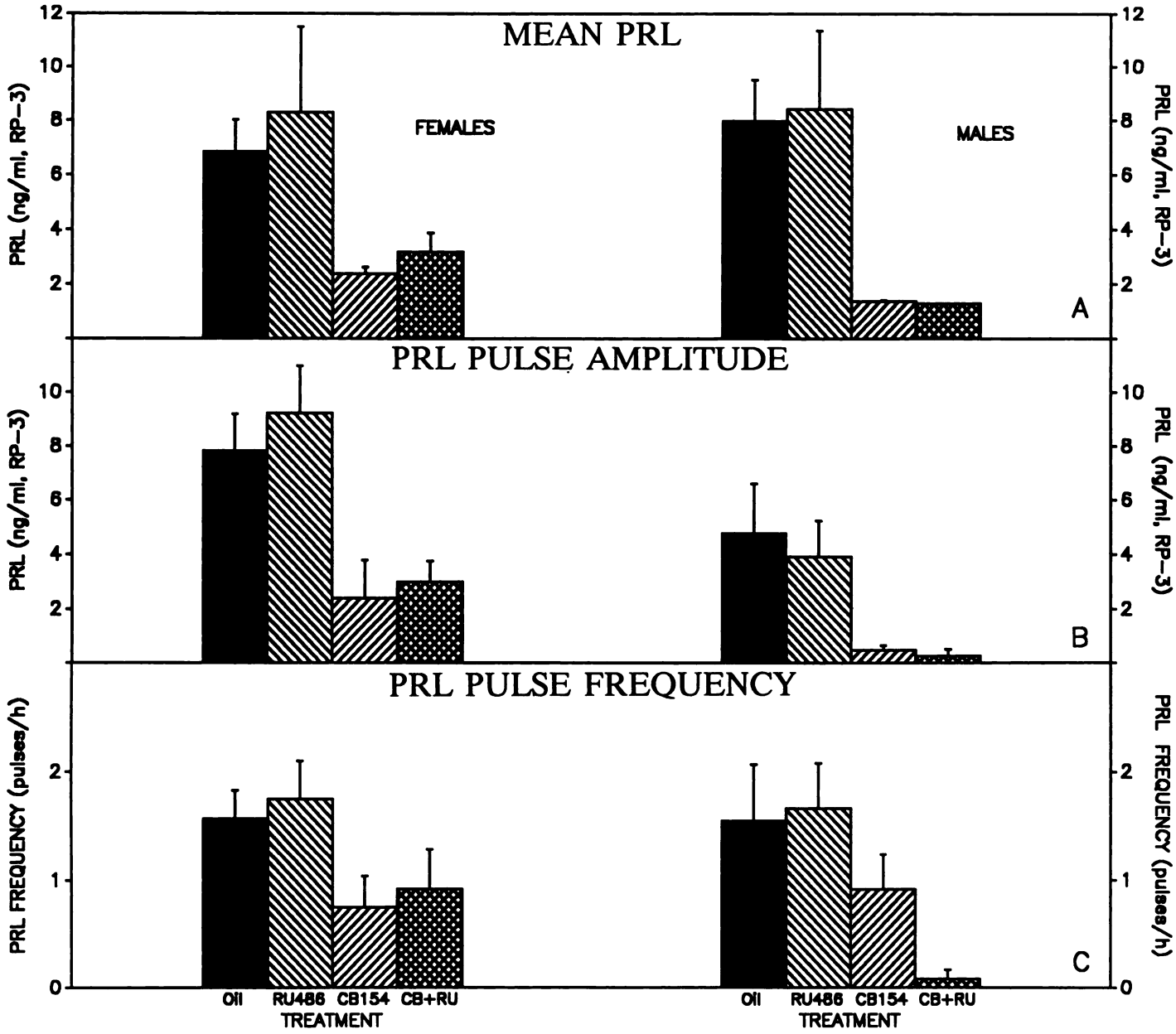

FIG. 5. Summary of pulsatile PRL release during 3-h serial blood sampling of females (left) and males (right) 24 h after gonadectomy. Treatment groups same as in Figure 4 (n = 4 per group). A: Mean ± SE PRL levels for each group. B: Mean ± SE of pulse amplitudes. C: Mean ± SE of pulse frequencies. Pulse amplitude was significantly higher in the females than in the males ($p < 0.002$). CB-154 alone or in combination with RU486 significantly suppressed all three parameters of PRL secretion ($p < 0.002$).

pletely reversed by testosterone administration alone [27]. A relatively greater role for inhibin in regulating FSH secretion in the female than in the male rat is also supported by studies in which the immunoneutralization of circulating inhibin in intact adult rats resulted in elevated FSH levels in females [28], but not in males [29].

The elevated PRL and P levels in all treatment groups during the first hour of blood sampling are in agreement with previous reports linking elevated PRL [30] and P [31] release to exposure to a stressor. There was an apparent trend for the males to have a more pronounced PRL elevation in response to the onset of serial sampling than the females. This was significant for both intact and gonadectomized animals. Interestingly, these high PRL and P levels did not appear to suppress LH pulsatility in animals of either sex. This stress effect on PRL secretion probably accounts for the higher PRL levels in males than in females during the first 2 h of blood sampling in experiment I. Other pub-

lished studies have demonstrated lower levels of PRL secretion in intact males than in cycling females [6–8]; however, PRL levels in metestrous and ovariectomized females and in intact and castrated males have been found to be quite similar [6, 8, 9]. This is in agreement with our finding that mean PRL levels during the third hour of blood sampling did not differ among groups.

Our results further demonstrate that the higher P [16, 17] and PRL [6, 7] levels during the estrous cycle of female rats do not account for the delayed LH rise following ovariectomy. Many studies have shown that hyperprolactinemia induced prior to gonadectomy can delay the postgonadectomy LH rise in male rats [12, 32] and can suppress LH in long-term and acutely ovariectomized rats [10, 11]. Although in our study a single s.c. injection of CB-154 was sufficient to suppress PRL pulse amplitude, frequency, and mean levels to nearly undetectable levels for 24 h, the suppression of PRL by CB-154 did not enhance pulsatile LH release in adult female (or male) rats at 24 h after gonadectomy. Dopamine (DA) has also been shown to alter LH secretion independently of its suppression of PRL secretion, but the direction of this effect remains controversial. In some studies, systemic administration of DA agonists [33] or intraventricular injection of DA itself [34] suppressed LH secretion in chronically ovariectomized rats, but had no effect in E-primed ovariectomized rats. In another study, intraventricular DA was found to stimulate LH secretion in E-primed rats, but to have no effect in untreated ovariectomized rats [35]. These differences may partially be related to the mode of DA administration employed: slow, constant infusion [34] versus pulse injection [35]. DA stimulation of in vitro GnRH release has also been observed [36]. Our finding of no change in LH secretion after systemic administration of a DA agonist in rats that had been deprived of E for only 24 h supports the finding that DA does not alter LH secretion in rats that have recently been exposed to high levels of circulating E [34]. Like PRL, exogenous P can suppress the elevated LH levels seen after ovariectomy [3, 16]; however, E coadministration is required to suppress LH to intact levels [3, 16], and larger doses of E alone can also suppress LH to intact levels [16]. Such results led us to speculate that endogenous P may be continuing to exert an acute suppressive effect on LH levels postovariectomy. The failure of suppression of endogenous P in the present experiments to accelerate the female's slow LH rise refutes this hypothesis.

What then is responsible for the female rat's slow rate of LH rise following ovariectomy? One hypothesis is that the last steroid to which the hypothalamic-pituitary axis is exposed determines the postgonadectomy LH response. Treatment of males with E and females with testosterone at the time of or just before gonadectomy [37, 38] followed by removal of the steroids at various intervals after gonadectomy resulted in rapid LH rises in males and slower rises in females, just as normally occurs after gonadectomy. The hypothesis that neonatal androgenization is responsible for the rapid LH response to gonadectomy has also been disproved. Neonatal treatment with the sex-opposite gonadal steroid results in attenuated gonadotropin responses to gonadectomy in both sexes, but does not reverse the sex difference in the LH response to gonadectomy [39]. Lorenzen and Ramaley [40] have shown that, before the first preovulatory LH surge, females, like males, respond to gonadectomy with a rapid LH rise, implying that the ability to have an LH surge in response to E may be linked to an inability to respond rapidly to the removal of negative feedback.

Recent experiments in our laboratory indicate that E exposure suppresses LH even after E is withdrawn [41]. Twenty-four-hour exposure of 3- or 7-day ovariectomized rats to proestrous E levels significantly suppresses LH pulse amplitude and frequency even 24 h after E implants have been removed and the plasma E concentration has fallen to ovariectomized levels [41]. This delayed response to E withdrawal is probably not caused by any lingering circulating E, and occupation of brain and pituitary E receptors also falls within 8–12 h [42]. We have shown that ovariectomy plus adrenalectomy plus administration of an E antagonist does not result in a more rapid LH rise than ovariectomy alone [43], suggesting that prolonged E receptor occupancy per se is not responsible for prolonged suppression of LH. Other prolonged actions of steroids, probably caused by a genomic action of the steroid, have been reported. E capsules implanted for 24 h induces afternoon LH surges for 3–5 days in ovariectomized rats [44]. In *Xenopus*, a single E treatment induces serum retinol binding protein mRNA for at least 125 days [45].

In summary, these results demonstrate (1) that at 24 h after gonadectomy the increase in pulsatile LH secretion in male rats is much greater than in females, while FSH levels increase similarly in both sexes and (2) that the higher PRL and/or P in cycling females does not contribute to the slow rate of LH rise in females after ovariectomy.

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