Regulations of gonadotropin secretion by circulating inhibin, estradiol, and progesterone in cyclic hamsters

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Kishi, Hisashi, Mariko Itoh, Ken-Ichi Ohshima, Ming-Wei Wang, Gen Watanabe, and Kazuyoshi Taya. Regulations of gonadotropin secretion by circulating inhibin, estradiol, and progesterone in cyclic hamsters. Am. J. Physiol. 277 (Endocrinol. Metab. 40): E876–E882, 1999.—The physiological importance of gonadal hormones in feedback control of gonadotropin secretion during the estrous cycle in golden hamsters was investigated with immunoneutralization methods. Anti-inhibin serum (inhibin-AS) treatment always induced a drastic increase in follicle-stimulating hormone (FSH) secretion and occasionally raised luteinizing hormone (LH) secretion. Anti-estradiol-17β serum (estradiol-AS) treatment increased LH secretion typically. Although estradiol-AS elevated FSH secretion occasionally, the elevation was much less than that by inhibin-AS. Plasma FSH reached ovarioctomized levels by a synergistic effect of both antisera. Elevated plasma LH with both antisera was much less pronounced than in ovarioctomized animals. Plasma LH increased dramatically to the levels in the ovarioctomized group when antibody against progesterone (progesterone-AB) was given together with inhibin-AS and estradiol-AS, although progesterone monoclonal antibody alone did not alter plasma gonadotropin levels. These results indicate that in hamsters FSH secretion is mainly regulated by inhibin and LH secretion is regulated by estradiol-17β and progesterone during the estrous cycle.

immunoneutralization; follicle-stimulating hormone; luteinizing hormone; estrous cycle; feedback

IT IS WELL KNOWN that gonadectomy causes the increase in plasma concentrations of gonadotropins in many species. In the golden hamster (Mesocricetus auratus), plasma concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) increase after ovariection (35), and gonadal steroid hormones have been thought to be primary factors in the regulation of gonadotropins (4, 11, 35, 36) in this species. It has been established that inhibin is a major inhibiting factor for FSH secretion in several species (6, 28). Recently, we demonstrated that plasma concentrations of inhibin fluctuate throughout the estrous cycle in the hamster and that the pattern of circulating inhibin shows an inverse relationship to that of FSH, suggesting that inhibin is the primary regulator of FSH secretion in the hamster as well as in other species (21). Administration of antiserum against inhibin in cyclic hamsters (20) and cyclic rats (1, 29) causes a dramatic increase in plasma FSH and in the spontaneous ovulation rate on day 1 of the next estrous cycle in the hamster. These observations suggest that inhibin regulates ovulation rate in these species by controlling secretion of FSH. However, it is still unclear as to how effectively endogenous inhibin regulates FSH secretion during the estrous cycle in the hamster, as plasma inhibin fluctuates during the ovarian cycle.

In the present study, we have investigated the role of endogenous inhibin, estradiol-17β, and progesterone in the release of gonadotropins by means of immunoneutralization at various stages of the estrous cycle of the hamster.

MATERIALS AND METHODS

Animals

Adult cyclic golden hamsters (Mesocricetus auratus) were kept under controlled temperature and lighting (lights on from 0500 to 1900). The 4-day estrous cycle was monitored by the presence of characteristic vaginal discharge on the morning of the day of ovulation, which was designated day 1 of the estrous cycle. Hamsters with at least two consecutive 4-day estrous cycles were used in this study.

Antiserum Against Estradiol-17β or Against Inhibin

Antiserum against estradiol-17β (estradiol-AS) was obtained from a castrated goat immunized against 1,3,5(10)-estratriene-3,17β-diol-6-one 6-(carboxymethyl)oxime conjugated to BSA (Steraloid, Wilton, NH) as described previously (1, 19, 21). In vivo efficiency of the estradiol-AS was studied by the increase in concentrations of LH in the plasma 6 and 12 h after a single intravenous injection of several doses of the antiserum at 1100 on day 3 of the estrous cycle in the cyclic hamster, when plasma concentrations of estradiol began to increase dramatically. The maximal increase in plasma concentrations of LH was shown when 100 µl or more estradiol-AS were treated (data not shown). Therefore, the amounts (100 µl) of estradiol-AS used in the present study were considered to be enough to block circulating estradiol-17β in the cyclic hamster. Antiserum against inhibin (inhibin-AS) was generated according to the method reported previously (1, 19–21, 34). Antigen for inhibin-AS [Tyr39-labeled inhibin α-chain(1–30) NH2 conjugated to rabbit serum albumin] was provided by Dr. N. Ling, Neurocrine Bioscience, San Diego, CA. In vivo efficiency of inhibin-AS was studied by evaluating the increase in plasma FSH after a single injection of several doses of the antiserum at 1100 on day 2 of the estrous cycle in the hamster.
the cyclic hamster, when plasma concentrations of inhibin reached plateau levels. These results have also been observed in a previous study (20). One hundred microliters of inhibin-AS used in the present study were considered to be enough to block the biological activity of circulating inhibin in the cyclic hamster. Control serum was obtained from a castrated goat.

Monoclonal Antibody to Progesterone

Monoclonal antibody to progesterone (progesterone-AB) used in this study was obtained as described previously (17). In brief, BALB/c mice were hyperimmunized with progesterone-11α-succinyl conjugated to BSA and their spleen cells were fused with mouse myeloma line NSO (38). Cross-reactivity of this monoclonal antibody (DB3) with a range of steroids was determined by competitive binding radioligand assay and has been reported elsewhere (8, 38). The affinity (Kd) of DB3 for progesterone was 0.24 nM (8). Hybridoma cells were grown as ascites in mice, and large-scale purification of the antibody from ascitic fluid was carried out on 18% sodium sulfate precipitation followed by ion-exchange chromatography on DE-32 cellulose. The purity was confirmed by SDS-polyacrylamide gel electrophoresis, isoelectric focusing, and immunoelectrophoresis (33). The amounts of progesterone-AB were determined by referring to the results demonstrated by Greenwald and Wang (17). In that study, 6.5 nM of progesterone-AB, which corresponded to the highest amounts used in the present study given to pregnant hamsters on day 4, terminated pregnancy in 78% of them by day 8. Therefore, the maximal amount (1 mg) of the antibody in the present study would neutralize most of the circulating progesterone in the cyclic hamster.

Effects of Inhibin-AS, Estradiol-AS, or the Combined Treatment on Gonadotropin Secretion at Various Stages of the Estrous Cycle

In this experiment, effects of immunoneutralization against inhibin and/or estradiol on gonadotropin secretion were investigated at five stages of ovarian status, based on previous studies (13–16, 21, 22). The five stages of ovarian status were as follows: 1) At 1100 on day 1, the ovary manifests no healthy antral follicles, but several small or medium-sized preantral follicles and newly formed corpora lutea are present. Plasma concentrations of inhibin and estradiol-17β are low, and plasma concentrations of progesterone are also low. 2) At 2300 on day 1, a few antral follicles appear in the ovary. Plasma concentrations of inhibin increase to a plateau level, which is maintained until the preovulatory surge, although plasma concentrations of estradiol-17β remain low. 3) At 1100 on day 2, the number of antral follicles increases and corpora lutea become functional. Plasma concentrations of estradiol-17β and progesterone begin to increase. 4) At 1100 on day 3, the number of antral follicles is maximal and signs of luteolysis appear. Plasma concentrations of inhibin and estradiol-17β are high and plasma concentrations of progesterone decline. 5) At 0500 on day 4, atretic signs appear in one-half of the antral follicles and corpora lutea vanish. Plasma concentrations of inhibin remain high, although plasma concentrations of estradiol-17β decline. Plasma concentrations of progesterone are undetectable.

Antiserum or control serum was injected (iv) once, under light ether anesthesia, into individual animals via the jugular vein at 1100 or 2300 on day 1, at 1100 on days 2 and 3, or at 0500 on day 4. Each injection volume was adjusted to 200 µl; for example, 100 µl of estradiol-AS and 100 µl of control serum were administered in the estradiol-AS treatment group and 200 µl of control serum were injected in the control group. Each group of animals was killed by decapitation at 6 or 12 h after the serum injection, and trunk blood samples were collected in heparinized centrifuge tubes. Blood samples were centrifuged immediately at 1700 g for 15 min at 4°C, and plasma was separated and stored at −20°C until assayed for FSH and LH.

A bilateral ovariectomy was performed on animals to deprive them of the ovarian factors under light ether anesthesia at 1100 or 2300 on day 1, at 1100 on days 2 and 3, or at 0500 on day 4. Each group of animals was killed by decapitation 6 or 12 h after the operation, and trunk blood samples were collected in heparinized centrifuge tubes. Plasma samples were obtained as described above and stored at −20°C until assayed for FSH and LH.

Effect of Progesterone-AB on the Secretion of Gonadotropins

Various doses of progesterone-AB (0.0625–1.0 mg progesterone-AB/200 µl PBS) were given to individual animals at 1100 on day 2 of the estrous cycle when plasma progesterone began to increase in the estrous cycle of the intact hamster (2, 21, 27). Each group of animals was killed by decapitation at 6 and 12 h after treatment, and trunk blood samples were collected. Plasma samples were obtained after centrifugation and stored at −20°C until assayed for gonadotropins. PBS (200 µl) was injected as control.

Effect of Combined Treatment with Inhibin-AS, Estradiol-AS, and Progesterone-AB on the Secretion of Gonadotropins

Combined treatment with both 100 µl inhibin-AS and 100 µl estradiol-AS or combined administration of 100 µl inhibin-AS, 100 µl estradiol-AS, and 1 mg progesterone-AB was undertaken at 1100 on day 2 of the estrous cycle. Plasma samples were collected at 6 and 12 h after treatment as described previously and stored at −20°C until assayed for FSH and LH. Control animals were given castrated goat serum in a similar manner, and ovariectomized hamsters were also used in this experiment.

RIAs for Gonadotropins

Plasma concentrations of FSH and LH were measured using National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) RIA kits for rat FSH and LH as described previously (3). Iodinated preparations were rat FSH-I-7 and LH-I-8. The antisera used were anti-rat FSH-S-11 and anti-rat LH-S-10. Results were expressed in terms of NIDDK rat FSH-RP-2 and rat LH-RP-2. The intra- and interassay coefficients of variation were 4.4 and 14.6% for FSH and 8.9 and 6.7% for LH, respectively.

Statistics

The values of plasma gonadotropin concentrations were expressed as means ± SE of five animals. The comparison of two means was made by the Student’s t-test or the Cochran-Cox test. The comparison among treatment groups was performed by one-way ANOVA, followed by Duncan’s multiple-range test (32). When there was heterogeneity of variance, the logarithmic transformation was carried out before ANOVA. Values of P < 0.05 were considered to be statistically significant.
RESULTS

Changes in Plasma Concentrations of FSH and LH After Treatment with Inhibin-AS, Estradiol-AS, or Both at Various Stages of the Estrous Cycle

Treatment at 1100 on day 1. Plasma concentrations of FSH after administration of inhibin-AS or combined treatment were significantly higher than in controls (Fig. 1, A and F). Plasma FSH after cotreatment with both inhibin-AS and estradiol-AS was increased further over that with injection of inhibin-AS alone; and the concentrations after combined treatment were similar to those observed in the ovariectomized group. On the other hand, treatment with estradiol-AS alone had little effect on plasma FSH. Slightly but significantly increased plasma FSH was noted 12 h after treatment in the group given estradiol-AS.

Plasma concentrations of LH were increased significantly 6 h after administration of estradiol-AS alone or combined treatment with inhibin-AS and estradiol-AS compared with controls, and they were similar to the levels in ovariectomized animals. However, the LH concentrations 12 h after treatment were significantly lower than those in the ovariectomized group, and there was no significant difference between plasma concentrations of LH in the various treatment groups (estradiol-AS alone, inhibin-AS plus estradiol-AS, or control serum).

Treatment at 2300 on day 1. Plasma concentrations of FSH were increased significantly after treatment with inhibin-AS alone or inhibin-AS plus estradiol-AS compared with the controls (Fig. 1, B and G). Administration of inhibin-AS in combination with estradiol-AS increased plasma FSH to a level that was higher than that found in animals treated with inhibin-AS alone but similar to that observed in the ovariectomized group. Treatment with estradiol-AS led to a modest but significant increase in plasma FSH when measured 6 h after treatment; FSH returned to control levels thereafter.

No effect of any antisera on plasma concentrations of LH was noted in this experiment. Plasma concentrations of LH after ovariectomy were significantly higher than after any treatment. The effect on LH was more pronounced 6 h after the ovariectomy performed at 2300 on day 1 of the cycle than that performed at 1100 on the same day.

Treatment at 1100 on day 2. Plasma concentrations of FSH increased significantly after administration of inhibin-AS alone or after combined treatment (inhibin-AS plus estradiol-AS; Fig. 1, C and H). Cotreatment markedly raised concentrations of FSH when compared with inhibin-AS alone; the values after treatment with

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Fig. 1. Changes in plasma concentrations of follicle-stimulating hormone (FSH; A–E) and luteinizing hormone (LH; F–J) at 6 and 12 h after treatment with control serum (●), anti-inhibin serum (inhibin-AS; ○), anti-estradiol-17β serum (estradiol-AS; △), both inhibin-AS and estradiol-AS (▽), or ovariectomy (○). Values are means ± SE of 5 animals. Within treatment group, Greek letters denote significant differences (P < 0.05 by Duncan’s multiple range test) among values at the same time.
both antisera were similar to those in the ovariectomized group 6 h after treatment. However, at 12 h after treatment, the ovariectomized group showed significantly higher levels of FSH than did the combined-treatment group.

Treatment with estradiol-AS as well as combined administration of inhibin-AS and estradiol-AS caused a significant increase in plasma concentrations of LH compared with the controls. Even higher plasma LH levels were noted after combined treatment, compared with estradiol-AS alone; however, this increase was attenuated in comparison with levels in the ovariectomized group. The impact on LH was greater when ovariectomy was carried out at 1100 on day 2 compared with that performed at 2300 on day 1 of the estrous cycle.

Treatment at 1100 on day 3. Significant increases in plasma FSH were found in all experimental groups when compared with the controls (Fig. 1, D and I). However, the values in the estradiol-AS-treated group were much smaller than those in other groups. Although plasma FSH after combined treatment was not higher than in the group given inhibin-AS alone when measured at 6 h after administration, it was markedly elevated thereafter.

All forms of treatment resulted in significant increases in plasma LH levels. At 12 h after treatment, a further increase was observed in the cotreatment group and the values were comparable to those in the ovariectomized animals.

Treatment at 0500 on day 4. Plasma FSH increased significantly at 6 h after treatment with inhibin-AS or a combination of inhibin AS and estradiol-AS but not after the treatment with estradiol-AS alone (Fig. 1, E and J). Combined treatment caused a greater FSH rise than that after inhibin-AS injection, and the level corresponded to that found in the ovariectomized group.

Plasma concentrations of LH did not change at 6 h after any antiserum treatment but were elevated by ovariectomy. At 12 h after treatment (except for inhibin-AS treated group), the surge levels of LH in the plasma declined significantly compared with the control levels. The impact of ovariectomy on plasma LH is less effective than that observed at 1100 on day 2 or 3.

Changes in Plasma Concentrations of FSH and LH After Treatment with Progesterone-AB at 1100 on Day 2

No alteration in plasma concentrations of FSH and LH was found after treatment with progesterone-AB, and their levels were similar to those after treatment with control serum (data not shown).

Changes in Plasma Concentrations of FSH and LH After Combined Treatment with Inhibin-AS, Estradiol-AS, and Progesterone-AB at 1100 on Day 2

Treatment with a combination of inhibin-AS, estradiol-AS, and progesterone-AB caused a significant increase in plasma concentrations of FSH and LH compared with the controls; the increased FSH concentrations were slightly higher than those after combined treatment with inhibin-AS and estradiol-AS and were similar to those in the ovariectomized group (Fig. 2). Plasma LH after combined administration of inhibin-AS, estradiol-AS, and progesterone-AB was increased over that of combined administration of inhibin-AS and estradiol-AS, and the levels corresponded to those observed after ovariectomy.

DISCUSSION

Immunoneutralization against inhibin caused a significant increase in the plasma concentrations of FSH and LH after combined administration of inhibin-AS, estradiol-AS, and progesterone-AB was increased over that of combined administration of inhibin-AS and estradiol-AS, and the levels corresponded to those observed after ovariectomy.

The morning of day 1 is the time just after ovulation, when mature follicles (which are thought to be the main source of circulating inhibin) do not exist in the ovaries (14, 21). Therefore, we believe that plasma concentrations of FSH were already high because of low plasma concentrations of inhibin, indicating that the immunoneutralization against inhibin during this stage does not induce further elevation of plasma FSH.

In the present study, the elevation rate in FSH concentrations in plasma after inhibin-AS treatment on the morning of day 1 was less than that after the treatment on other cycle days, compared with rats (1). The morning of day 1 is the time just after ovulation, when mature follicles (which are thought to be the main source of circulating inhibin) do not exist in the ovaries (14, 21). Therefore, we believe that plasma concentrations of FSH were already high because of low plasma concentrations of inhibin, indicating that the immunoneutralization against inhibin during this stage does not induce further elevation of plasma FSH.

The small stimulation of FSH secretion by immunoneutralization against estradiol-17β was also observed on day 1 or 3 but not on day 2 or 4. This time the discrepancy in results might come from the changing pattern in plasma concentrations of estradiol-17β during the estrous cycle of hamsters. Based on our previous report (21), plasma estradiol-17β enters a first incremental phase from the morning of day 1 and a second incremental phase from the morning of day 3. On the other hand, it enters a first decremental phase from the morning of day 2 and a second decremental phase from the morning of day 4. Plasma concentrations of inhibin have already reached their zenith levels by the night of day 1. Therefore, it may be difficult to distinguish the effect of estradiol-AS itself given on days 2 and 4 from that of decreased circulating estradiol-17β in the control group when FSH secretion is suppressed by high levels of plasma inhibin. A large dose of
estradiol suppresses plasma concentrations of FSH in ovariectomized hamsters (4, 35, 36). Estradiol inhibits the postcastration rise in FSHβ-subunit mRNA in the rat (10). Passive immunization of estradiol-17β causes the elevation of plasma concentrations of FSH in rats (1) and sheep (24). These reports also support our contention that estradiol-17β acts as a negative regulator of FSH secretion.

In the present study, further increases were observed most of the time in plasma concentrations of FSH in the animals treated with both inhibin-AS and estradiol-AS, compared with those in animals treated with inhibin-AS alone (as well as in a rat study with the same antisera; Ref. 1). The amount of inhibin-AS used in the present study is thought to be enough to cause maximal increment in plasma FSH (20). These findings suggest that the action of estradiol-17β on the suppression of FSH secretion may be different from that of inhibin. Inhibin is generally thought to act on the pituitary directly. On the other hand, it is thought that negative effects of estradiol-17β act on hypothalamus rather than on pituitary (7, 30, 31). Therefore, additive stimulation caused by inhibin-AS and estradiol-AS is thought to be the mode of inhibin action, via suppression of FSH production by the pituitary and the action of estradiol-17β in suppression of gonadotropin-releasing hormone (GnRH) secretion for the hypothalamus. It is also reported that estradiol-17β directly regulates FSH secretion from the pituitary and has the ability to suppress FSH secretion in the ovine pituitary cell culture system (26). On the other hand, the levels of FSH after treatment with both antisera were comparable to those after ovariectomy, suggesting that inhibin and estradiol-17β in the plasma regulate FSH secretion negatively in the cyclic hamster.

Plasma concentrations of FSH 12 h after cotreatment with both antisera on day 3 were higher than those after ovariectomy, suggesting that ovarian factors that stimulate FSH secretion, such as activin, might play a small role in regulating the secretion of FSH during this time.

When estradiol-AS was administered to the cyclic hamster, plasma LH increased in most of phases studied, compared with the respective controls. As demonstrated in previous reports (4, 35, 36), the present results indicate that circulating estradiol-17β is an important negative regulator of basal LH secretion during the estrous cycle of hamsters. In many cases in the present study, however, plasma concentrations of LH after immunoneutralization against estradiol-17β were much lower than those after ovariectomy.

A synergistic effect on basal levels of LH was found when inhibin-AS was superimposed on estradiol-AS at 1100 on day 2 or 3 of the estrous cycle. In this case,
inhibit-AS alone can also cause an increase in the basal plasma levels of LH. These observations suggest that circulating inhibit may act as a regulator of LH secretion, at least on days 2 and 3 of the estrous cycle. It is still arguable whether inhibit itself is involved in the secretion of LH in female rats. Rivier and Vale (29) demonstrated that circulating inhibit does not alter rat LH secretion by using antiserum against inhibit, whereas other studies (1, 5) show that endogenous inhibit suppresses LH secretion. Previous work (19, 20) also shows that immunoneutralization of inhibit on day 2 or 3 of the estrous cycle raises (temporally but significantly) plasma concentrations of LH in the cyclic hamster. These discrepancies may be related to the potency of antiserum used in each experiment. This consideration can be supported by our previous report (20) in which treatment with 50 µl or more, but not 25 µl or less, antiserum against inhibit caused an increase in plasma LH (although 12.5 µl of the same antiserum already led to a maximal increase in plasma concentrations of FSH). Farnworth et al. (9) demonstrated that purified bovine inhibit suppresses LH as well as FSH release with a rat pituitary cell culture system. Wang et al. (37) reported that purified bovine inhibit decreases the number of specific binding sites for GnRH on rat anterior pituitary cells in vitro. These findings suggest that inhibit appears to be a putative regulator of LH secretion in the cyclic hamster.

The present study suggests species differences in the stimulatory effect of cotreatment with estradiol-AS and inhibit-AS on basal LH secretion. The elevated levels of plasma LH after both antisera were clearly lower than those after ovariectomy in the hamster, unlike the rat (1). This suggests that the regulation of basal LH secretion in the hamster is different from that in the rat. Although no effect was shown by treatment with progesterone-AB alone on plasma concentrations of gonadotropins, the levels after immunoneutralization against three hormones (inhibit, estradiol-17β, and progesterone) on the morning of day 3 corresponded to those after ovariectomy. This observation suggests that progesterone plays an important role as a negative regulator of basal LH secretion in the hamster only when it acts in synergy with estradiol-17β and inhibit.

Vomachka and Greenwald (35, 36) demonstrated that cotreatment with both estradiol and progesterone is more effective in the suppression of the ovariectomy-induced elevation in plasma LH than treatment with either separately. In addition, Goodman and Karsch (12) showed the effect of ovarian steroids on the profiles of the pulse secretion of LH, suggesting that estradiol-17β and progesterone could inhibit LH secretion by completely different mechanisms through the modification of the pulse of GnRH. These results may support the present findings that progesterone plays a cooperative role in the presence of estradiol-17β on LH secretion. At the same time, the synergistic effect of progesterone-AB on inhibit-AS and estradiol-AS action was also found in the increase in FSH secretion, although the effect was slight. This finding suggests that progesterone would be a negative regulator of FSH secretion, as well as LH, in the cyclic hamster.

Another species difference between the hamster and the rat was observed in the gonadal regulation of LH secretion on day 1. Plasma concentrations of LH increased after ovariectomy on day 1 of the cycle in the hamster. On the other hand, in the rat, elevation of concentrations of LH in the plasma was not observed until at least 24 h after ovariectomy on the morning of estrus (1), which corresponded with day 1 in the hamster. One possibility of this species difference may come from the difference between relative importance of estradiol-17β in the hamster and the rat during this period. Plasma LH in the hamster increased after treatment with estradiol-AS or cotreatment with estradiol-AS and inhibit-AS on the morning of day 1, but this increase in plasma LH after treatment with estradiol-AS on the morning of estrus was not observed in the rat (1).

In the present study, when estradiol-AS was given with or without inhibit-AS, or ovariectomy was performed on the morning of day 4, the LH surge was clearly diminished compared with the control group. Although peak LH was lower, surge did occur in all experimental groups on the afternoon of day 4 as well as in the control group. This effect of ovariectomy agrees with previous studies (11, 35), indicating that estradiol-17β on the morning of day 4 is required to elicit a normal LH surge. Norman and Spies (25) demonstrated that the diurnal LH elevation via hypothalamus was induced 1 day after estrogen treatment. Therefore, the present study also demonstrates that induction of the LH surge was already established due to increased levels of plasma estradiol-17β until the morning of day 4.

In conclusion, plasma FSH concentrations in the hamster are primarily regulated by circulating inhibit, and a synergistic effect of estradiol-17β was noted during the estrous cycle of this species. Circulating estradiol-17β mainly regulates plasma concentrations of LH during the estrous cycle of the hamster, and circulating progesterone may also play an important role in suppressing tonic levels of LH in the hamster.

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