J. steroid Biochem. Vol. 27, No. 4–6, pp. 665–675, 1987
Printed in Great Britain. 

0022-4731/87 $3.00 + 0.00


Proceedings of the VII International Congress on Hormonal Steroids (Madrid, Spain, 1986)

**19. Integration of Steroid and Neurotransmitter Systems in the Brain**

# INTEGRATION OF THE EFFECTS OF ESTRADIOL AND PROGESTERONE IN THE MODULATION OF GONADOTROPIN SECRETION

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**Summary**—Estradiol secreted by the maturing follicle is the primary trigger for the surge of gonadotropins leading to ovulation. Progesterone has stimulatory or inhibitory actions on this estrogen-induced gonadotropin surge depending upon the time and dose of administration. The administration of progesterone to immature ovariectomized rats primed with a low dose of estradiol induced a well-defined LH surge and prolonged FSH release, a pattern similar to the proestrus surge of gonadotropins. A physiological role of progesterone is indicated in the normal ovulatory process because a single injection of the progesterone antagonist RU 486 on the day of proestrus in the adult cycling rat and on the day of the gonadotropin surge in the pregnant mare's serum gonadotropin stimulated immature rat resulted in an attenuated gonadotropin surge and reduced the number of ova per ovulating rat. Progesterone administration brought about a rapid LHRH release and an decrease in nuclear accumulation of estrogen receptors in the anterior pituitary but not the hypothalamus. The progesterone effect was demonstrated *in vitro* in the uterus and anterior pituitary and appears to be confined to occupied estradiol nuclear receptors. In *in vivo* experiments the progesterone effect on estradiol nuclear receptors appeared to be of approximately 2-h duration, which coincided with the time period of progesterone nuclear receptor accumulation after a single injection of progesterone. During the period of progesterone effects on nuclear estrogen receptors, the ability of estrogens to induce progesterone receptors was impaired. Based on the above results, a model is proposed for the stimulatory and inhibitory effects of progesterone on gonadotropin secretion.

## INTRODUCTION

The regulation of events in the higher brain centers and the pituitary gland by estradiol and progesterone culminating in a gonadotropin surge leading to ovulation is complex and has been a subject of extensive investigation. The concept that estradiol produced by the maturing ovarian follicle is the primary trigger for the preovulatory gonadotropin surge is now well established in a number of animal species including man. Progesterone has been shown to be stimulatory or inhibitory to gonadotropin release depending upon the dose, the time of administration and the estrogenic milieu present. Progesterone metabolites have been shown to bring about a selective release of either LH or FSH and there is mounting evidence that progesterone plays a physiological role in modulating the estrogen-triggered ovulatory surge. The roles of estradiol and progesterone and their integrative interactions in the modulation of gonadotropin secretion leading to the preovulatory surge of gonadotropins will be reviewed in this paper.

## ESTROGEN EFFECTS ON GONADOTROPIN SECRETION

It is well recognized that estrogens exert both a positive and negative feedback effect on gonadotropin secretion. Since the comprehensive review of the subject by Everett in 1964 [1] a number of papers have appeared in the literature describing the negative and positive feedback systems in considerable detail.

The presence of the negative feedback system was established by the classical experiments demonstrating that ovariectomy resulted in elevated secretion of LH and FSH which could be suppressed by estrogen replacement. Detailed studies in the intact animal have shown that the administration of estrogens invariably results in the initial lowering of gonadotropins followed by the manifestation of a positive feedback effect several hours later[2]. In addition to the hypothalamus, the negative and positive feedback effects of estrogens can be manifested directly at the level of the pituitary as shown by experiments with pituitary cells in culture [3, 4].

The role of estrogens in triggering the preovulatory surge of gonadotropins has also been demonstrated conclusively by several lines of evidence. Ovariectomy in rats, hamsters and sheep before the day of proestrus abolishes the preovulatory surge of gonadotropins and the administration of estradiol or estradiol benzoate reinstates at least a partial surge [5–14]. The administration of antibodies to estradiol or estradiol antagonists also abolish the gonadotropin surge [15–17]. The ability of estradiol to elicit LH surges similar to the preovulatory surge of gonadotropins is also well documented [18–24]. It has been shown that enhanced sensitivity of the pituitary to LHRH in the release of gonadotropins is one of the mechanisms of the estrogen-induced gonadotropin surge [22, 24–33]. The work of several

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investigators has shown that the continued presence of the estrogen trigger is not necessary on the day of proestrus and ovariectomy on the day of proestrus does not abolish the gonadotropin surge. This has been confirmed in a detailed study by Ashiru and Blake [34]. Furthermore, it has been demonstrated that there is a fall in circulating estradiol during the gonadotropin surge. If this fall is prevented by the implantation of Silastic capsules of estradiol, the magnitude of the gonadotropin surge is decreased [35, 36].

The uptake of [$^3$H]estradiol in various cells of the pituitary and various regions of hypothalamus and the presence of estrogen-binding proteins which display the characteristics of receptors in those tissues have been reported by several investigators [37–42]. Since an estrogen stimulus is considered to be the primary trigger for the surge of gonadotropins leading to ovulation, a study of estrogen receptor dynamics during the rat ovulatory cycle was undertaken [40, 43]. Acute depletion of cytoplasmic estrogen receptors of the hypothalamus and anterior gland occurred on the day of proestrus in the cycling rat. Previous studies with estrogen-sensitive tissues had already established that estrogen-induced cytoplasmic receptor depletion correlates well with nuclear translocation of the estrogen–receptor complex [44]. This nuclear translocation of the estrogen–receptor complex in the hypothalamus and the anterior pituitary correlated well with the endogenous gonadotropin surge and increased responsiveness of the pituitary gland to LHRH. Such a relationship between estrogen receptor translocation and the gonadotropin surge was also observed in the natural onset of puberty and in pregnant mare's serum gonadotropin (PMSG) induced ovulation in the immature rat [45, 46]. The direct effect of estradiol on the increased sensitivity of the anterior pituitary to LHRH-induced LH release has already been cited on the basis of indirect *in vivo* evidence in intact animals, evidence obtained in pituitary stalk-sectioned rats and *in vitro* studies in dispersed pituitary cell cultures. The hypothalamic effect appears to be LHRH release shown *in vivo* in the rat [47], sheep [48] and monkey [49] and in *in vitro* superfusion studies using hypothalamic tissue [50–52].

## PROGESTERONE MODULATION OF GONADOTROPIN SECRETION

The experiments of Everett in 1948 [53] clearly showed that progesterone could have a stimulatory effect or an inhibitory effect on gonadotropin secretion related to the time of administration of progesterone in the ovulatory cycle. When progesterone was given within a few hours of the preovulatory gonadotropin surge in the cycling animal or the estrogen induced LH surge in ovariectomized animal, its effects were stimulatory. Progesterone given at earlier time periods in the cycle or in estrogen-treated ovariectomized rats was inhibitory to the gonadotropin surge. The facilitative [31, 53–59] and inhibitory [53, 57–62] effects of progesterone on gonadotropin secretion are now well recognized in laboratory animals. In the human, attention to the stimulatory effect of progesterone on gonadotropin secretion in an estrogen-treated menopausal woman was first drawn by Odell and Swerdloff in 1968 [63]. This observation was subsequently confirmed by others [64, 65]. In contrast, the inhibitory effects of progesterone on gonadotropin secretion are also well documented in monkeys and the human [66–68]. The administration of progesterone before the peak levels of estradiol are reached in the cycle prevents the estrogen-induced gonadotropin surge and large quantities of progesterone significantly shorten the duration of the LH surge [24, 69].

The work of several investigators has shown that estrogen priming of the ovariectomized animal is essential for progesterone to exert its action on gonadotropin secretion [54, 58, 70, 71]. Estrogen priming of the ovariectomized rat in the form of single injections of 5–50 $\mu$g of estradiol or estradiol benzoate or a Silastic implant of estradiol results in the induction of multiple daily surges of LH [13, 14, 72–75]. Progesterone administration shortly before the estrogen-induced surge is facilitative. Beyond this first surge or if given at other times, progesterone brings about an extinction of the daily surges of LH induced by estrogens [60, 61]. Furthermore, once progesterone is administered for 13 h, the daily LH surge pattern in response to a 33-h exposure to estradiol via Silastic implants in the long-term castrated rat is abolished for a period of 8–10 days [62].

### *An animal model for the study of the action of progesterone*

The study of the effect of progesterone in the cycling rat is difficult because the stimulatory and inhibitory effects are dependent upon the time of administration in relation to the preovulatory surge of gonadotropin [53]. Similar disadvantages are also present in the ovariectomized rat primed with doses of estradiol that result in an LH surge. The long-term effects of progesterone [62] are also of concern. Therefore in our studies, we established an immature ovariectomized rat model which was injected with low doses of estradiol every 12 h [58, 59, 76]. The characteristics sought in this model were lowering of serum LH and FSH by about 50% as compared with ovariectomized control, so that both the stimulatory and inhibitory effects of progesterone could be observed, the absence of a estrogen-induced gonadotropin surge and the induction of progesterone receptors in the hypothalamus and the pituitary to ensure progesterone sensitivity. These characteristics were met by using the immature female rat ovariectomized at day 26 of age and treated with 0.1 $\mu$g/kg body wt of

estradiol per day in two equally divided doses for 4 days [58, 59, 76, 77]. The injection of various doses of progesterone in combination with 0.1 μg/kg body wt of estradiol for 5 days [58] or as a single injection after 4 days of estrogen priming [59] brought about a surge of LH and FSH with 0.2 or 0.8 mg/kg body wt of progesterone and no change or suppression with the 0.4 or 3.2 mg/kg body wt of progesterone. Thus, these experiments established that progesterone could induce an ovulatory type surge of gonadotropins in the properly estrogen-primed animal and that the stimulatory and inhibitory action was related to the dose as well.

The question whether the experimental model was relevant to the secretion of gonadotropins in the rat ovulatory cycle was further answered by an examination of the gonadotropin patterns in serum and the anterior pituitary of rats given a single injection of progesterone [59]. Serum LH levels returned to baseline by 6 p.m. while serum FSH levels remained elevated into the night when the stimulatory dose of progesterone administered. This was similar to what is found on proestrus in the cycling rat [78]. This selective release of FSH over LH occurred even though pituitary LH was elevated in addition to FSH. The selective release of FSH by the progesterone metabolite 5α-dihydroprogesterone [79, 81] and the selective release of LH by 3α, 5α-tetrahydroprogesterone [80, 81] has also been demonstrated using the immature estrogen-primed or pregnant mare's serum gonadotropin-primed rate model.

*The physiological role of progesterone in modulating the estrogen-induced ovulatory surge of gonadotropins*

The ability of progesterone to induce a gonadotropin surge in the estrogen-primed rat has been described above. Other investigators have also demonstrated that the full gonadotropin surge in ovariectomized animals treated with estrogen is dependent on progesterone [10, 56, 82]. A rise in progesterone in serum [83] and ovarian vein blood [84] in rats has been observed on the day of proestrus prior to the rise of LH. Therefore, a physiological role of progesterone in the process of ovulation is strongly indicated. To further confirm the role of progesterone in modulating the preovulatory gonadotropin surge, the progesterone antagonist RU 486 was used [85]. A single injection of RU 486 resulted in a decrease in the number of ova per ovulating rat and an attenuation of the FSH and LH surge in the adult rat and the PMSG-primed immature rat. These observations confirmed a physiological role of progesterone in modulating the gonadotropin surge in the normal ovulatory process. The role of progesterone in bringing about a rapid release in LH and FSH and manifesting the full gonadotropin surge has also been indicated by studies in the monkey and the human [24, 63–65, 69, 86–89].

## SITES OF ACTION OF PROGESTERONE IN THE MODULATION OF GONADOTROPIN SECRETION

The mechanisms by which progesterone exerts its regulatory influences on gonadotropin secretion which are dependent on the time of administration as well as the dose of progesterone used, are complex and poorly understood. These actions of progesterone are progesterone receptor mediated events because, if estrogen priming of the ovariectomized animal to induce progesterone receptors is not carried out, progesterone is unable to alter gonadotropin secretion. The most obvious sites of action of progesterone would appear to be (a) release of hypothalamic LHRH, (b) an alteration in LHRH receptors or binding affinity of LHRH to its receptors in the anterior pituitary and (c) the integration of progesterone and estrogen effect by progesterone modulation of estrogen receptor dynamics involved in gonadotropin release.

*Release of hypothalamic LHRH induced by progesterone*

The alterations in pituitary sensitivity to LHRH induced by progesterone [59] may be due to alterations in the endogenous LHRH secretory patterns rather than a direct effect on the pituitary because the self-priming effect of LHRH on the pituitary is well documented [22, 90–92]. The immature ovariectomized rat primed with 0.1 μg/kg body wt of estradiol provided an excellent opportunity to study the dose-related stimulatory and inhibitory effects, or the lack of effect of progesterone on hypothalamic LHRH and LHRH release [76]. The stimulatory dose of progesterone (0.8 mg/kg body wt) brought about a rapid increase in medial basal hypothalamic LHRH and plasma LHRH within 30 min of administration with further evidence of LHRH release immediately preceding the LH surge. Such a change was not observed with the 3.2 mg/kg body wt dose of progesterone which did not alter serum LH. Thus, a dose-related effect of progesterone on LHRH release was established. Evidence of LHRH release induced by progesterone has also been obtained by other investigators in *in vivo* studies, using push–pull cannulae and superfused hypothalamic tissue [50–52, 93–95]. Direct effect of progesterone on estrogen primed pituitary cells in augmenting LHRH-induced gonadotropin release has also been reported [96, 97].

*Alterations in anterior pituitary LHRH receptors by estrogens and progesterone*

In considering a direct modulatory role of progesterone on the sensitivity of the pituitary to LHRH, possible mechanisms could include modulation of LHRH binding affinity and/or induction of new LHRH receptors in the pituitary gland. A number of investigators have studied the changes occurring in LHRH receptors during the rat estrous cycle [98–100] using LHRH analogs for determining the bind-

ing affinity and concentration of binding sites on pituitary plasma membranes. Increased levels of receptors for LHRH were found during the period of metestrus and diestrus but no acute changes were observed on proestrus during the time when the pituitary gland shows maximum sensitivity to LHRH. These results are in agreement with previous work in which no difference in LHRH receptor numbers was found in ovariectomized rats and sheep during the period when estrogen administration sensitized the pituitary to LHRH[101–103]. The dependence of pituitary LHRH receptor induction on LHRH and estradiol [104–106] and a decrease in such receptors induced by progesterone [107] have also been demonstrated.

*Integration of progesterone and estrogen effects by progesterone modulation of estrogen receptors*

The work of Turgeon and Barraclough [35] and Turgeon [36] suggested that, on the day of proestrus in the rat, the circulating levels of estradiol played an important role in the magnitude of the LH surge. If the falling levels of estradiol during the surge were prevented by the administration of Silastic estradiol implants, the LH surge was attenuated. It was therefore of interest to study the effect of progesterone on anterior pituitary and hypothalamic estrogen receptor dynamics. For this purpose, the immature ovariectomized rat primed with 0.1 $\mu$g/kg body wt of estradiol was used. A single injection of 0.8 mg/kg body wt of progesterone 1 h prior to a 5 $\mu$g dose of estradiol to promote nuclear accumulation of the estrogen receptor resulted in a decrease in anterior pituitary nuclear estrogen receptors with no change in hypothalamic nuclear receptors [77]. This effect of progesterone was apparently mediated through its receptor because it was not observed in the absence of estrogen priming to induce the progesterone receptor. The tissue specificity of the nuclear estrogen receptor suppression is difficult to explain. It is, however, of interest to note that 17$\beta$-hydroxysteroid dehydrogenase activity was stimulated by progesterone in the anterior pituitary but not the hypothalamus [108].

In order to investigate further the progesterone modulation of estrogen receptor dynamics, studies were done *in vitro* (Smanik, Calderon, Muldoon and Mahesh, unpublished data). Adult female rats were ovariectomized. They were killed 2 weeks later and the anterior pituitaries and the uteri were homogenized and separated into cytosol and nuclear fractions. The cytosol and nuclear fractions were divided into four groups. The fractions in Group 1 and Group 2 did not receive any treatment. Group 3 cytosol received no treatment while the nuclear fraction was incubated with 0.25 nM progesterone at 4°C for 30 min. In Group 4, the cytosol was incubated with progesterone while the nuclei did not receive any treatment. All cytosol fractions were then treated with dextran–charcoal and all nuclear fractions were washed 3 times to remove free steroids. The cytosol and nuclear fractions in each group were recombined in the absence (Group 1) or the presence (Groups 2, 3 and 4) and 3 nM estradiol at 22°C for 1 h. After separation of cytosol and nuclei and removal of the free steroids by dextran–charcoal and washing, estrogen receptors were determined in each fraction. The results in Fig. 1 show the expected depletion of cytosol receptors and accumulation of nuclear receptors induced by estradiol in the uterus and in the anterior pituitary (Group 1 vs Group 2). Irrespective of whether progesterone was added to the nuclei (Group 3) or to the cytosol (Group 4), it brought about a significant decrease in the nuclear estrogen receptor accumulation in the uterus and the anterior pituitary (Groups 3 and 4 vs Group 2), while cytosol receptors were unaffected. These results confirm the effect of progesterone observed *in vivo* on nuclear estrogen receptor accumulation. The mechanisms involved, however, are poorly understood and are under further study.

It is now recognized that both occupied and

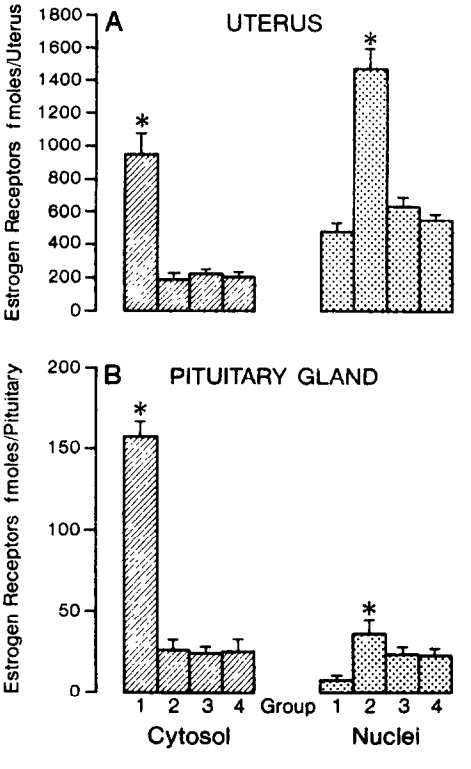


Fig. 1. Cytosol and nuclear estrogen receptors in uterine and anterior pituitary fractions after recombination in the absence (Group 1) or the presence (Groups 2, 3, 4) or 3 nM estradiol at 22°C for 1 h.The nuclear fraction in Group 3 and the cytosol fraction of Group 4, were pretreated with 0.25 nM progesterone at 4°C for 30 min. The free steroids were removed from the cytosol with dextran–charcoal and the nuclei by washing prior to the recombination with or without estradiol. The cytosol and nuclear fractions were reseparated, the free steroids removed and the estrogen receptors determined. *Significant difference ($P < 0.05$) from other fractions.

unoccupied receptors of steroids may be present in the cytosol and the nuclei. In order to determine which estrogen receptor population was affected to result in the decreased nuclear accumulation observed, the *in vitro* experiments were repeated with measurements of the unoccupied cytosol receptors at 4°C for 18 h (non-exchange conditions), total cytosol receptors at 22°C for 17 h followed by 4°C for 1 h (exchange conditions), unoccupied nuclear receptors at 4°C for 16 h (non-exchange conditions) and total nuclear receptors at 37°C for 30 min (exchange conditions). The results in Fig. 2 show that, in uterine tissue, treatment of the cytosol with progesterone resulted in the selective inhibition of the nuclear accumulation of occupied estrogen receptors (Group 4 vs Group 2).

The above experiments indicated acute modulation of nuclear estrogen receptor accumulation of progesterone *in vitro* and *in vivo*. Occupied nuclear receptor populations are considered to be involved in regulatory functions and the modulation of estrogen receptor activity by progesterone thus has the potential of an important regulatory step in the control of gonadotropin secretion. A review of the literature shows that there is no general agreement

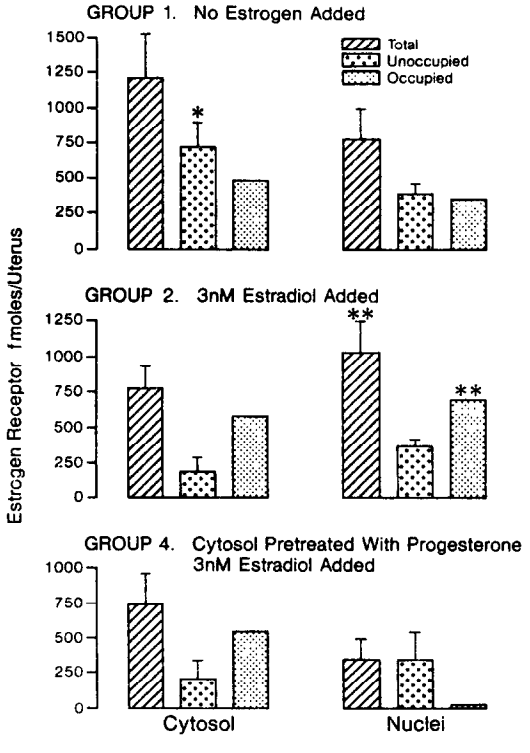


Fig. 2. Total and unoccupied estrogen receptors in uterine homogenates in Groups 1, 2 and 4 of Fig. 1. Unoccupied receptors were measured in the cytosol and nuclear fractions by using nonexchange conditions while total receptors were measured under exchange conditions. The difference between the two represents occupied receptors. *Significant difference ($P < 0.05$) from same fraction in Group 2 and 4; **significant difference ($P < 0.05$) from same fractions in Group 4.

on the effects of progesterone on estrogen receptors in the hypothalamus and the pituitary. The work of several investigators has shown no progesterone effects [109–113]. Our earlier publication [77] shows a tissue-specific effect of progesterone on estrogen receptors of the anterior pituitary which have been confirmed by the *in vitro* studies described above. Blaustein and Brown[114] have also reported an effect of progesterone on pituitary and hypothalamic estrogen receptors.

In an attempt to explain the above-mentioned discrepancies, in all probability due to the variety of animal models and experimental conditions used in different studies, further investigations were carried out in the ovariectomized rat *in vivo* (Calderon, Muldoon and Mahesh, unpublished results). The time course of progesterone receptor induction in the hypothalamus and the anterior pituitary in the immature rat ovariectomized on day 23 of age was studied at 4-h intervals after a bolus of 2 μg of estradiol on day 24 of age. The cytoplasmic progesterone receptor concentration rose steadily in the hypothalamus and the pituitary reaching a maximum at 12 h with a plateau thereafter (Fig. 3). Nuclear progesterone receptor concentration was either undetectable or very low. Injections of 0.8 mg/kg body wt of progesterone were given 12 h after the estradiol injection and cytoplasmic and nuclear progesterone receptors were measured at 0, 1, 2, 4 and 8 h after the progesterone injection. Nuclear accumulation of progesterone was found at the 1-h (data not shown) and 2-h interval in the anterior pituitary and 1-, 2- and 4-h interval in the hypothalamus (Fig. 3).

In the next set of experiments, female rats were ovariectomized on day 23 of age. On day 24 they received an injection of 2 μg of estradiol followed by an injection of progesterone 12 h later. A second injection of 2 μg estradiol was administered 1, 2 and 6 h for the measurement of cytoplasmic and nuclear estrogen receptors in the anterior pituitary and the hypothalamus. The results showed no change in cytosol receptors in either tissue as a result of progesterone treatment. A decrease in nuclear estrogen receptor accumulation occurred in the anterior pituitary at 1 and 2 h after progesterone administration with no change occurring in hypothalamic nuclear receptors (Fig. 4). In a subsequent experiment in May (previous experiment was done in November) the time points studied were 1 and 3 h after progesterone administration. The decrease in the nuclear estrogen receptor accumulation in the anterior pituitary was confirmed at 1 h after progesterone administration with no change at 3 h. Of considerable interest was the increase in total receptor numbers in May as compared to November, which may represent seasonal variability which has been observed in other receptor systems. Overall these results confirm the tissue-specific effect of progesterone on pituitary nuclear estrogen receptor

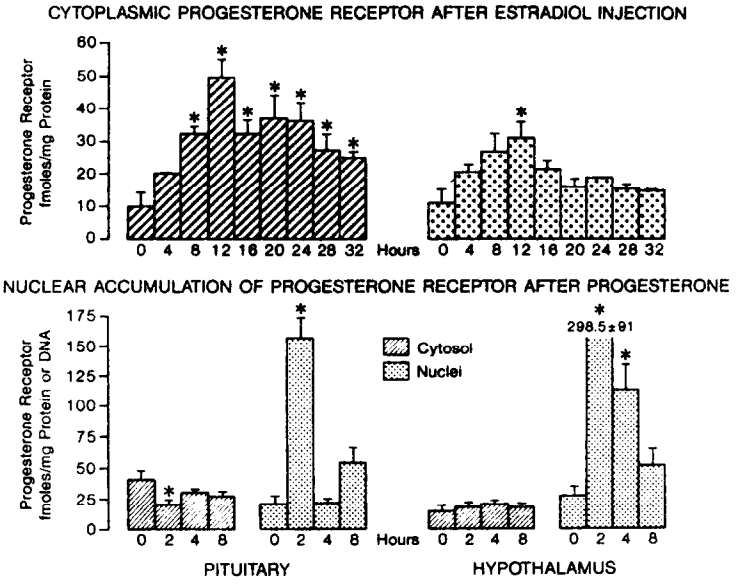


Fig. 3. Top panel shows progesterone cytosol receptors in 24-day-old female rats, 1 day after ovariectomy and at 4-h intervals after a single injection of 2 $\mu$g estradiol. *Significant difference ($P < 0.05$) from control values. Bottom panel shows cytosol and nuclear progesterone receptors in ovariectomized-estrogen primed rats at various time intervals after a single injection 0.8 mg/kg body wt of progesterone, 12 h after estradiol priming. *Significant difference ($P < 0.05$) from other fractions.

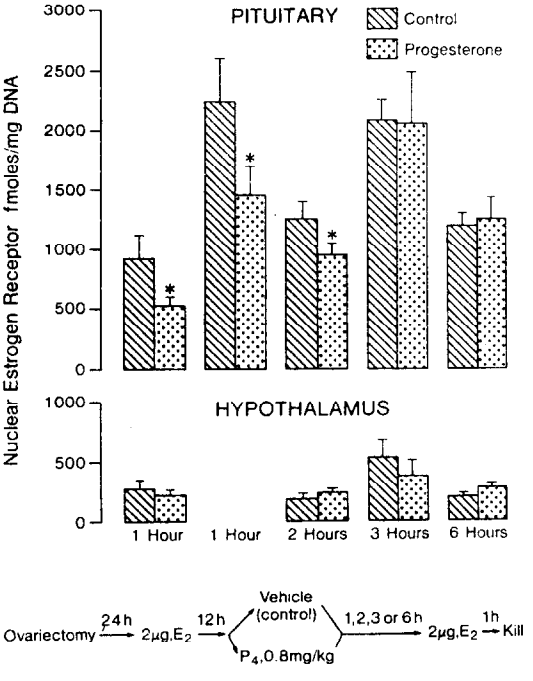


Fig. 4. Nuclear estrogen receptors of the anterior pituitary and hypothalamus in ovariectomized rats primed with 2 $\mu$g estradiol, injected 0.8 mg/kg body wt of progesterone 12 h after estradiol and given a second injection of 2 $\mu$g estradiol 1, 2, 3 and 6 h after progesterone. The animals were killed 1 h after the second injection of estradiol for receptor determinations. *Significant difference ($P < 0.05$) from respective controls. The second 1-h determination and the 3-h determination was done in May while other experiments were done in November.

accumulation reported by us earlier [77]. Furthermore, the duration of the effect appears to be similar to the duration of increased progesterone nuclear receptor retention after the injection of progesterone.

The above observations raise the question whether the decrease in nuclear estrogen receptor accumulation in the anterior pituitary by progesterone plays a functional role. An answer to this question was sought by studying the progesterone receptor induction by estradiol. The experimental protocol consisted of using the ovariectomized estrogen- and progesterone-treated animal model and giving a second injection of vehicle or estradiol 1 or 4 h after the progesterone injection. Cytoplasmic progesterone receptors were measured 12 h after the second estrogen or vehicle injection. The results in Fig. 5 show that progesterone injection 1 h before the second estradiol injection blocked the second estrogen-induced rise in progesterone receptors while progesterone injected 4 h before did not have any effect. These results confirm that progesterone-induced decrease in nuclear estrogen receptor accumulation in the pituitary interferes with the biological effects of estradiol.

### A MODEL ENCOMPASSING THE STIMULATORY AND INHIBITORY EFFECTS OF PROGESTERONE

The regulation of gonadotropin secretion by progesterone is complex and includes effects of the dose of progesterone, the time of administration, its

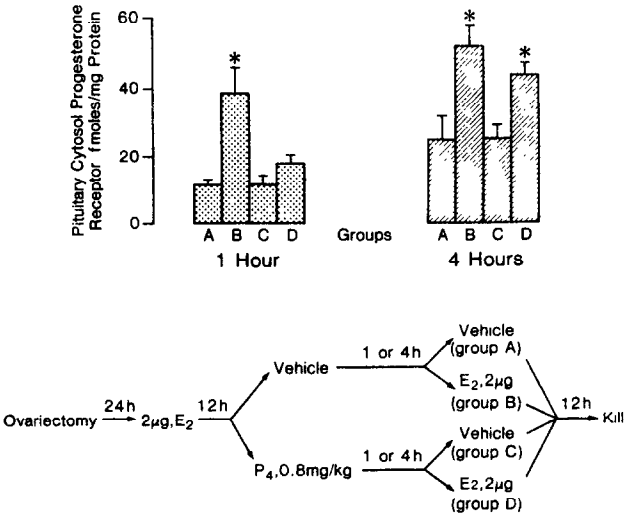


Fig. 5. Induction of cytosol progesterone receptors by a second injection of estradiol in ovariectomized estrogen treated rats with (Group D) or without (Group B) progesterone pretreatment 1 or 4 h before the second estradiol injection. *Significant difference ($P < 0.05$) from other values.

influence on pulsatile LHRH discharge and its effects on LHRH-degrading enzymes. The results reported in this paper along with the literature in the field permit proposal of a model for the stimulatory and inhibitory effects of progesterone depending upon the time of administration involving the integration of estrogen and progesterone interaction in the regulatory process (Fig. 6). Pituitary LHRH receptors are regulated by the self-priming effect of LHRH in the presence of estradiol (A). Pituitary sensitivity to LHRH in the release of LH is reduced acutely by estrogens (B) and enhanced as a long-term estrogen effect (C). Estrogens also induce progesterone receptor synthesis in the hypothalamus and the pituitary (D) and bring about hypothalamic LHRH release (F) as a long-term effect. Progesterone may have a direct effect on the sensitivity of the pituitary to LHRH (E) and bring about a rapid release of hypothalamic LHRH (G) and a decrease in LHRH degrading enzymes (H) (O'Conner, personal communication; [115]). When progesterone is administered in conditions of appropriate estrogen priming, progesterone antagonism of long-term estrogen effects (A, C, D and F) does not play a significant inhibitory role. Its antagonism of the acute inhibitory effects of estradiol (B), the rapid release of LHRH (G), decrease in LHRH degradation (H) and possibly a direct effect on the pituitary gland's sensitivity to LHRH (E) create conditions optimal for a gonadotropin surge. When progesterone is administered at an inappropriate estrogen primed state, its antagonism of steps A, C, D and F creates inhibitory conditions. Furthermore, the steps B, G, H and E would be limited by progesterone receptor availability resulting in an overall inhibition of gonadotropin secretion.

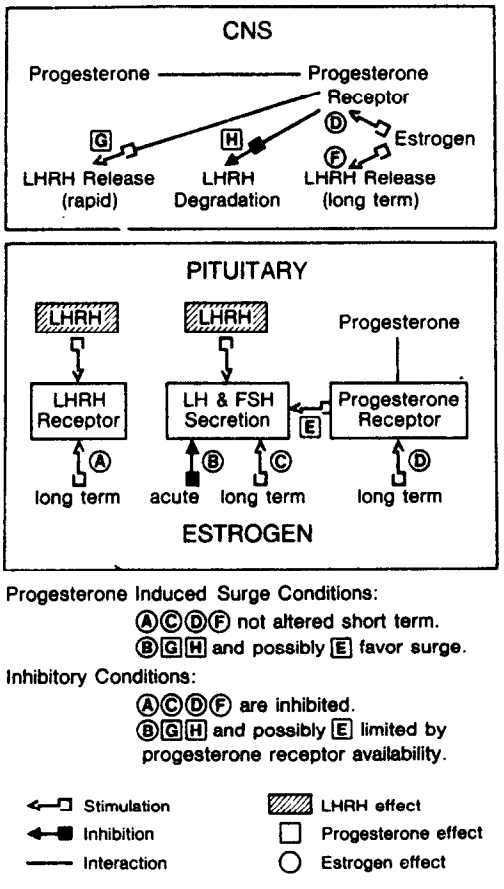


Fig. 6. A model to explain stimulatory and inhibitory effects of progesterone on gonadotropin secretion. This first model does not consider the dose-dependent effects of progesterone and its effect on the pulsatile discharge of LHRH.

*Acknowledgement*—This investigation was supported by research grant HD 16688 from the National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

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