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PROGESTERONE AND SEXUAL BEHAVIOR IN MALES

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SUMMARY

Previous investigations into the effects of progestins on copulatory behavior have suggested that progesterone inhibits the expression of androgen-dependent sexual behaviors in males. However, virtually all of those studies utilized pharmacological dosages of progesterone. Such experiments, although essential for understanding the behavioral effects of progesterone, yield little insight into the function of endogenous progesterone in masculine sexual responses. In this brief review, attention is focused on the role of physiological levels progesterone in copulatory behavior in male reptiles and mammals. Efforts are made to promote a reevaluation of the behavioral effects of progestins in males, similar to ongoing studies which are reexamining neural mechanisms involved in progestin-mediated reproductive behavior in the female.

Keywords—Progesterone; Sex behavior; RU 486; Rats; Lizards.

INTRODUCTION

OVER THE YEARS an extensive literature has accumulated on the role of progesterone (P) in female reproduction. Recent data would suggest that progesterone acts on neural tissue via nongenomic, as well as genomic, mechanisms both of which appear to be involved in the expression of female sexual behavior. Investigators are currently localizing the neuroanatomical areas regulating these distinct neural mechanisms. Yet, little information is available on the functional aspects of this gonadal/adrenal hormone in males. Previous studies indicated that pharmacological dosages of progesterone can inhibit sexual behavior in males. However, more recent experiments suggest that physiological levels of progesterone may have an opposite effect, stimulating masculine copulatory behavior. These results raise the question as to whether physiological levels of progesterone have the capacity to modulate androgen-dependent sexual behavior in males, as it similarly modulates estrogen-dependent sexual receptivity in females. This paper summarizes recent data on species-specific responses to physiological levels of progesterone and its role in the expression of copulatory behavior in males.

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PROGESTERONE REGULATION OF REPRODUCTIVE BEHAVIOR IN FEMALES

The effects of progesterone on sexual behavior in females are well documented in mammals. Briefly, progesterone acts synergistically with estrogen to facilitate lordosis and is essential for the species-typical expression of proceptivity (soliciting the male) and sexual receptivity in estrogen-primed females (Fadem et al., 1979; Tennent et al., 1980). Classically, the actions of progesterone, as well as other sex steroid hormones, are mediated by a ligand-dependent transcription factor, or receptor, which when activated by a hormone directly affects gene transcription (Evans, 1988). The behavioral effects of progesterone in females are thought to be mediated by estrogen-inducible progesterone receptors (PR) located within the medial preoptic area (MPOA) and ventromedial nucleus of the hypothalamus (VMN) (Sar & Stumpf, 1974; Warembourg, 1992), brain regions known to regulate female reproductive behavior (reviewed in Pfaff & Schwartz–Giblin, 1988).

However, recent studies suggest that in other brain regions progesterone may facilitate sexual behavior through both genomic and nongenomic mechanisms (Delville, 1991; Frye et al., 1992). Intracranial implantation of progesterone into the VMH and the ventral mesencephalon significantly facilitates sexual receptivity in hamsters (DeBold & Malsbury, 1989; Pleim et al., 1990). This finding along with the discovery of membrane binding sites for progesterone (Towle & Sze, 1983), and the subsequent development of protein-conjugated progestin ligands as experimental tools (Ke & Ramirez, 1990), has prompted new investigations into the mechanisms by which progesterone modulates sexual behavior in females. For example, it was recently demonstrated that progesterone conjugated to bovine serum albumin, which does not diffuse freely through the plasma membrane, enhances sexual receptivity in hamsters by actions on cell membranes within the ventral tegmental area, and not the hypothalamus (Frye et al., 1992).

PROGESTERONE REGULATION OF REPRODUCTIVE BEHAVIOR IN MALES

The role of progesterone in modulating androgen-dependent sexual behavior in males is more ambiguous. It is generally accepted that in rats masculine sexual behavior is regulated by testicular testosterone acting in the MPOA via its metabolites, dihydrotestosterone (DHT) and estrogen (E) (reviewed in Sachs & Meisel, 1988). Along with intracellular conversion of testosterone to other androgens, neurons in the MPOA have the capacity to aromatize testosterone to estradiol (Roselli et al., 1985), which ultimately affects genomic expression and subsequent reproductive behavior. Both testicular testosterone and the MPOA are essential for the full expression of masculine sexual behavior in a variety of species (reviewed in Sachs & Meisel, 1988).

Progesterone receptors have been localized in several diencephalic nuclei including the MPOA and hypothalamic nuclei in male rats (Brown et al., 1987). In fact, no sex differences in progesterone receptor distribution (Lauber et al., 1991a) or concentration (Brown et al., 1987) have been found within the MPOA, although sex differences in receptor concentration in the VMN and arcuate nucleus have been reported (Brown et al., 1987; Lauber et al., 1991b). In male rats, progesterone is secreted by the adrenals and possibly the testes in a circadian pattern, with peak levels of progesterone being greater than five times nadir levels (Kalra & Kalra, 1977). Interestingly, peak progesterone

levels coincide with the onset of the dark phase of the photoperiod, a time when typical sexual activity is most intense in the male rat. Given the involvement of the MPOA in the control of sexual behavior, the presence of progesterone receptors in this region, and the circadian rhythm of progesterone in the male, the issue of a physiological role of progesterone in the regulation of sexual behavior in males deserves attention.

Several experiments, dating back to 1966, have demonstrated that pharmacological dosages of progesterone can and do inhibit androgen-dependent sexual behavior in diverse species such as guinea pigs (Connolly & Resko, 1989), mice (Erpino, 1973), quail (Bottoni et al., 1985), ring doves (Erickson et al., 1967), pigeons (Erpino, 1969), monkeys (discussed in Bonsall et al., 1990). Synthetic progestins, such as medroxyprogesterone acetate (MPA) or cyproterone acetate, have even been used clinically on human males to suppress sexual activity for prolonged periods of time (Bradford, 1988; Lehne, 1988). Despite our limited knowledge on the role of progesterone in humans, progestin therapy has been used routinely as a means to control libido in felony sex offenders. Most of the currently used therapeutic progestins have strong anti-androgenic properties.

The above studies indicate that pharmacological dosages of progesterone interfere with the ability of androgens to maintain or restore copulatory behavior in intact or castrated males that are sexually experienced. Several mechanisms for the antiandrogenic effects of pharmacological dosages of progestins have been proposed, including increased androgen catabolism in the liver (Albin et al., 1973), decreased uptake of androgens in target tissue (Stern & Eisenfield, 1971), inhibition of testosterone reduction to DHT in target tissue (Martini, 1982) and interference with the androgen receptor mechanisms (Connolly & Resko, 1989). Since the injections of large dosages of progesterone in the studies mentioned above likely produced supraphysiological concentrations of circulating progesterone, it is difficult to draw conclusions from their results regarding the physiological role of endogenous progesterone in modulating sexual behavior in males.

Two studies, which have investigated the effects of progesterone on sexual behavior in males, present some results which are particularly interesting. Erpino (1973) reported that in intact mice, 0.5 and 1.0 mg of progesterone significantly inhibited mounting and intromission behavior. However, the lowest dose in that study, 0.25 mg/day of progesterone, resulted in a slight, but not statistically significant, increase in mounting and intromission behavior. Also Debold and co-workers (DeBold et al., 1978) reported that simultaneous injections of progesterone and testosterone proprionate (TP) were more successful (though again not statistically significant) than TP alone at maintaining sexual behavior in castrated hamsters. From these results, it is apparent that further experimentation with physiological dosages of progesterone are needed to elucidate the physiological role of progesterone in males.

RECENT STUDIES: PROGESTERONE MODULATION OF SEXUAL BEHAVIOR IN MALE REPTILES

Recent comparative studies in reptiles have provided evidence that a link between progestins and male sexual behavior does exist in some vertebrates. This relationship was initially discovered in *Cnemidophorus uniparens*, an all-female species of parthenogenetically reproducing whiptail lizards. Although there are no males in this species, parthenogens alternate between expressing female-like receptive behavior during vitellogenisis and male-like mounting and copulatory behavior following the time of ovulation. This male-like pseudosexual behavior serves to facilitate ovarian development in the

recipient, as does male courtship in most sexual species (Crews et al., 1986). The peak in progesterone secretion associated with ovulation facilitates the expression of male-like "pseudosexual" behaviors (Grassman & Crews, 1986). This alternation between sexual receptivity and mounting/copulatory behaviors makes this species a particularly interesting model for understanding the neural mechanisms underlying sexuality since each individual's brain manifests both feminine and masculine sexual behaviors over the course of several days.

In little striped whiptail lizards (*C. inornatus*), a sexual ancestor of *C. uniparens*, androgens are involved in the expression of mounting and copulatory behaviors. However, exogenous progesterone can also restore the full complement of sexual responses in some castrated males (Lindzey & Crews, 1986). The effects of exogenous progesterone are abolished with concomitant treatment with the synthetic progesterone antagonist RU 486 and mimicked with the nonmetabolizable progestin agonist R5020 (Lindzey & Crews, 1988) (see Fig. 1A). It was subsequently demonstrated that low dosages of progesterone act synergistically with subthreshold levels of androgens (DHT) to reinstate courtship behavior in castrated *C. inornatus* males (Lindzey et al., 1988; Lindzey & Crews, 1992) (see Fig. 1B).

Since all previous reports indicated a general phenomenon of antiandrogenic effects of progesterone on sexual behavior in males, the question immediately arose as to whether *Cnemidophorus* spp. had evolved a unique neuroendocrine pathway by which progesterone exhibited androgenic effects rather than antiandrogenic effects. To answer this question, the effects of progesterone were investigated in males of another unrelated lizard, the green anole (*Anolis carolinensis*). The results of this study demonstrated that although high levels of progesterone can inhibit sexual behavior in the intact male (in agreement with the earlier studies), progesterone can also act synergistically with exogenous androgens to reinstate courtship behavior in castrated males (Young et al., 1991). This synandrogenic effect of progesterone reinstatement of sexual responses suggested that the phenomenon was not unique to whiptails and may be expressed in other reptilian species. The above experiments provoked a renewed interest in progesterone's actions on androgen-dependent sexual behavior in other vertebrates such as mammals.

RECENT STUDIES: PROGESTERONE MODULATION OF SEXUAL BEHAVIOR IN MALE RATS

Parallel studies in rats have aroused speculation concerning the role of progesterone in modulating sexual behavior in some mammals. Although there may be species-specific differences in behavioral responses to progesterone, the method of administration (acute vs. chronic) or dosage (pharmocological vs. physiological) may differentially affect brain mechanisms that play a significant role in the expression of these behavioral responses. Results from the reptile studies led us to examine the effect of physiological dosages of progesterone in gonadectomized male rats to determine the potency of this steroid in the initiation of male reproductive behavior (Witt et al., 1994).

In brief, we used sexually naive male rats that were castrated and 2 weeks later implanted with silastic capsules that were either empty (B, 10 mm and 30 mm in length) or packed with testosterone (T, 30 mm length, i.d. 0.078 mm, o.d. 0.125 mm), progesterone (P, 10 mm length, i.d. 0.04 mm,), or both T and P (P+T, in separate capsules). After 1 week, these males were given a 15-min test with an estrous female and their behavioral responses, plasma hormone levels, and seminal vesicle weights were compared to gonad-

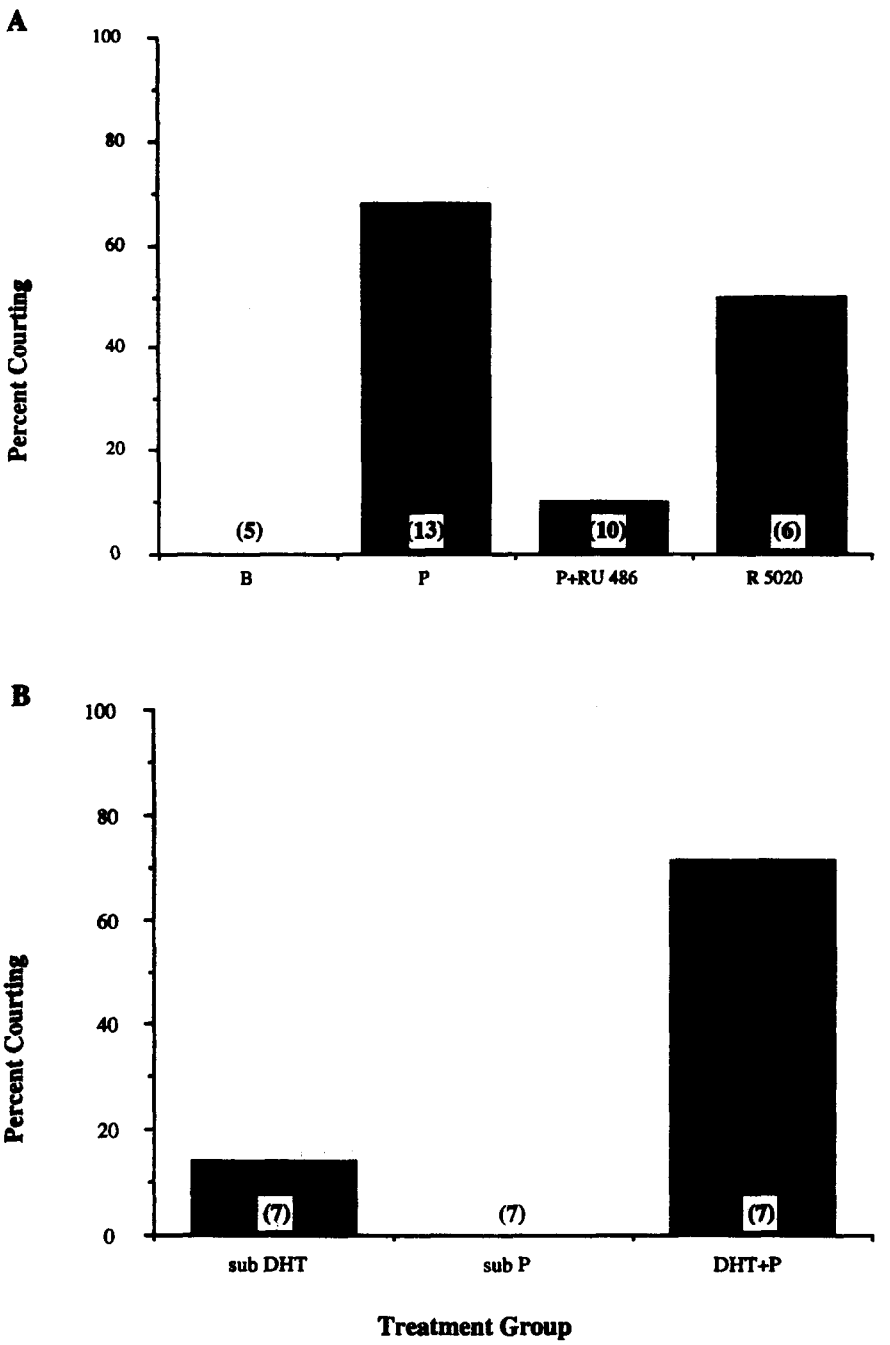

FIG. 1: (A) Figure illustrates the percent of castrated male *C. inornatus* exhibiting courting behavior after receiving an empty silastic capsule (B) or capsules filled with progesterone alone (P), progtesterone and RU 486 (P+RU 486) or (progestin agonist) R 5020 alone. (B) Synergistic interactions of subthreshold dihydrotestosterone treatment (DHT), and subthreshold progesterone treatment (P) in castrated male *C. inornatus*.

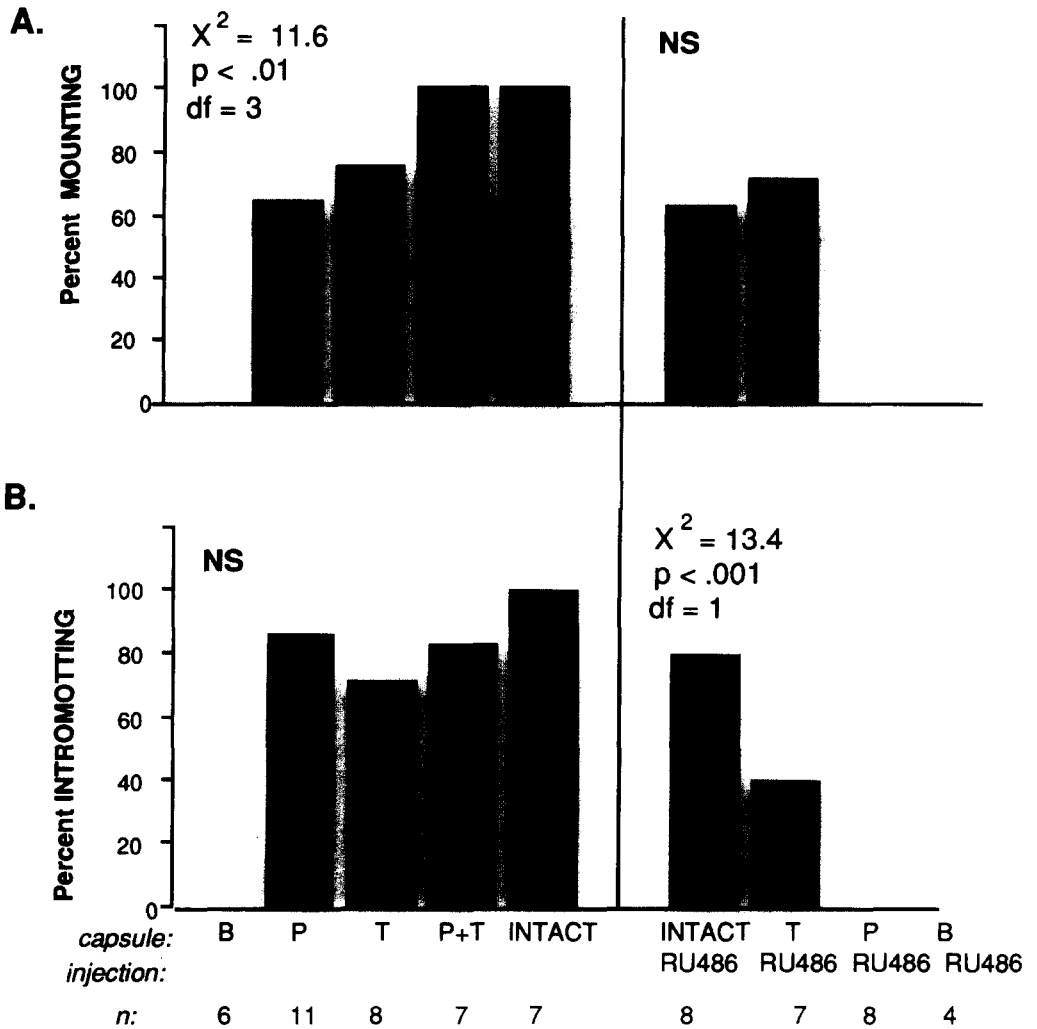

FIG. 2: Percentages of sexually naive male rats exhibiting mounting behavior (A) and subsequent intromission responses (B). Chi-square evaluations are based only on groups containing males that were sexually active, showing both mounting and intromission responses.

ally intact males (INTACT). It should be noted that as castration does not abolish endogenous P, our P treatment should be considered a supplementation of the endogenous P levels. The mean progesterone levels of each group as measured by radioimmunoassay are as follows: 3.2 ng/ml for B males; 5.1 ng/ml for P males, 1.5 ng/ml for INTACT males. These P levels in our INTACTS and castrates and the increase in P levels after castration are similar to those previously reported for males rats (Piva et al., 1973).

As expected, all of the INTACT males mounted (Fig. 2A) and intromitted (Fig. 2B) successfully while none of the castrated controls (B) exhibited copulatory behavior. T-treatment alone resulted in 75% of the castrated males mounting and only 83% of these males intromitted successfully. Surprisingly, 64% of the castrated males receiving P

supplementation exhibited mounting behavior and 86% of these males intromitted successfully during copulatory interactions (see Fig. 2). Furthermore, when P was added to the T-treatment (P+T) 100% of the males exhibited mounting behavior and 71% of these males intromitted successfully. In most cases males that exhibited typical mounting behavior also displayed normal intromission responses. On closer examination, the sexually active males revealed few, if any, differences in the actual frequency of mounting or intromission behavior.

Exogenous testosterone in sexually naive male rats frequently does not cause a uniform response as some androgen-treated males will not exhibit sexual behavior when presented with an estrous female. In our study, T alone was insufficient in restoring normal sexual responses in all males unless P levels were elevated. Indeed, we found that P initiated sexual behavior even in the absence of T. Therefore, the role of P was further examined in gonadally intact males, and castrated males implanted with either P, T, or Blank capsules, all of which received daily injections of the progesterone antagonist RU 486 (2 mg/kg per day).

RU 486 {11β-(4-dimethylamino phenyl)-17β-hydroxy-17α-(1-propynyl)-4,-9-estradien-3-one} is perhaps the most extensively studied progesterone antagonist. In vivo and in vitro models have shown that this ligand effectively antagonizes cytosolic progestin receptors and is devoid of agonist activity (Philibert et al., 1991). In addition, RU 486 has antiglucocorticoid effects along with moderate antiandrogenic properties (Moguilewsky & Philibert, 1985). RU 486 has virtually no interactions with mineralocorticoid or estrogen receptors, and has been characterized as having relative binding affinities (RBA) in the order of 530 for progesterone receptors, 300 for glucocorticoid receptors, and 23 for androgen receptors (Moguilewsky & Philibert, 1985).

Of the gonadally intact males receiving RU 486 treatment, only five of eight males successfully mounted (Fig. 2A) and only four successfully intromitted (compared to 100% in intacts receiving no treatment) (Fig. 2B). In T-treated castrates receiving RU 486 treatment, five of seven mounted and only two successfully intromitted. And finally, the facilitatory effects of P on copulatory behaviors were completely abolished by RU 486 treatment, with none of the males mounting or intromitting.

DISCUSSION

Although early investigations suggested that progestins inhibit the expression of androgen-dependent reproductive behaviors in males, new data from the present studies using more physiologically relevant levels of progesterone indicate otherwise. This effect was first observed in reptiles. In the parthenogen *Cnemidophorus uniparens*, endogenous progesterone appeared to facilitate mounting behavior in the absence of androgens. These observations led to the discovery that progesterone can facilitate sexual behavior in males in two other species of lizards.

In lizards, the paradoxical effects of progesterone stimulation/inhibition of reproductive behavior indicate two things: (1) the neuroendocrine pathways by which progesterone facilitates male sexual behavior are not unique to *Cnemidophorus* spp.; and (2) the antiandrogenic effects of pharmacological dosages of progesterone in other vertebrates may not refect of the effects of endogenous progesterone. The results from experiments using reptiles had provoked a renewed interest in progesterone's actions on androgen-dependent sexual behavior in other vertebrates such as mammals.

Based on the findings in lizards, we were prompted to conduct similar experiments

in rats. This is the first study to date in which the focus has been on the effects of physiological levels of progesterone on sexual behavior in a male mammal. Our results demonstrate that minor supplementation of the endogenous progesterone in castrated male rats is capable of initiating the full complement of sexual behavior. Furthermore, administration of the synthetic antiprogestin RU 486 inhibited the expression of sexual behavior in some gonadally intact male rats and completely abolished the facilitatory effects of progesterone supplementation. This suggests that progestins, rather than progesterone metabolites, are modulating these behavioral responses. Furthermore, the RU 486 antagonism of the progesterone-mediated sexual behavior in our study suggests that the nuclear progesterone receptor, and not some other receptor, is modulating these behavioral responses.

We cannot entirely rule out the possiblity that RU 486 may be working on glucocorticoid or androgen receptor mechanisms to produce these behavior effects. Based on plasma hormone measurements, we are confident that the dosage used in the our study, (2 mg/kg per day), was not sufficient to exert significant antiglucocorticoid or antiandrogenic effects. The antiglucocorticoid effects of RU 486 would have resulted in increased release of ACTH followed by increased corticosterone levels. There were no differences in corticosterone levels in any of our treatment groups. In vivo studies have shown that RU 486 does not inhibit corticosterone synthesis that is stimulated by ACTH in rat adrenal cells (Philibert et al., 1985). However, this ligand does exert moderate antiandrogenic effects as reflected in seminal vesicles and prostate weights (Philibert et al., 1985). In our study, any significant antiandrogenic effects of the RU 486 treatment would have been apparent by a reduction in the androgen stimulated seminal vesicle weight or alterations in plasma testosterone levels. No such differences were apparent. It should also be noted that when RU 486 was administered chronically to female rats for 15 days (3–30 mg/kg per day), no antiovulatory activity was observed (Philibert et al., 1985); however, dose-dependent increases were detected in serum LH and progesterone concentrations (Philibert et al., 1985). Interestingly, in our study, all groups receiving RU 486 treatment also exhibited increases in plasma P concentrations. These results indicate that under our treatment paradigm using RU 486, any effect on sexual behavior is most likely due to the blocking of PR-mediated actions and not interference with either glucocorticoid or androgen receptor-mediated mechanisms.

In conclusion, these data suggest that progesterone may play an important role in the normal expression of androgen-dependent sexual behavior in male reptiles and mammals. We do not know whether our behavioral effects, in both species, were a result of genomic or nongenomic actions, or perhaps a combination of these two neuronal features. Clearly, more extensive studies must be performed to understand the neural mechanisms underlying the effects of progesterone in the male.

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