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INDUCTION OF PROGESTIN RECEPTORS IN THE MEDIOBASAL HYPOTHALAMUS OF GONADALLY INTACT MALE RATS PRIMED WITH ESTROGEN IN RELATION TO DISPLAY OF LORDOSIS BEHAVIOR

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Summary—The purpose of this study was to determine whether the effects of estrogen on lordosis behavior in the male rat were related to the number of progesterone (P) receptors in the mediobasal hypothalamus (MBH) and/or dependent on blood P concentration. Two groups of gonadally intact male rats were given five successive doses of 1.0 or 2.5 μg estradiol benzoate (EB) and tested for lordosis behavior with a male stimulus at the end of the treatment. One month later they were again injected with EB and sacrificed under the same temporal schedule, but they were not tested for lordosis so as to prevent any emotionally stressful effects of intermale cohabitation. The males given 2.5 μg EB more frequently displayed lordosis responses to male mounts than those receiving 1 μg EB, with a parallel increase in the number of MBH P receptors. The total number of MBH P receptors also appeared to be higher in the animals that displayed lordosis responses (lordosis group) than in those which did not (no lordosis group). In contrast, the display of lordosis behavior was negatively correlated with blood P concentration.

Comparing MBH P receptors and blood P values in the EB treated and in nonhormonally treated gonadally intact animals which had been selected for either ability or inability to spontaneously display lordosis behavior, we observed that (1) EB was capable of increasing the number of MBH P receptors in the male rat; and (2) in the absence of EB treatment blood P values were higher in the animals showing lordosis than in those which did not. These data are discussed with respect to observations made in castrated male rats and in ovariectomized females.

INTRODUCTION

The induction of lordosis behavior by estrogen in the male rat has been clearly established during the two last decades [1–4]. In contrast, the possibility of facilitating estrogen induced lordosis behavior by progesterone (P) remains a debated question. Although present in the female [5–7], this possibility has been generally thought to be absent in male rats castrated in adulthood [8–11]. Opposite results have been reported, however, suggesting that exogenous P might facilitate estrogen induced lordosis behavior in male rats castrated as adults [3, 4, 12–14] and also in intact male rats [3]. Endogenous P of adrenocortical origin also appeared to be capable of facilitating lordosis in both castrated [15] and intact [16] adult male rats.

The ventromedial nucleus (VMN) of the hypothalamus plays a key role in the control of lordosis behavior in the female [17] and in the male [18] rat and estradiol (E_2) receptors are known to be present in the mediobasal hypothalamus (MBH)—where the VMN is located—in both males and females [for review see Ref. 19]. Constitutive P receptors have also been detected, although only in small numbers, in the MBH of castrated male hamsters [20] and rats [21, 22]. Nevertheless the ability of estrogen to induce P receptors in the hypothalamus is still a matter of controversy at the present time. E_2 induction of P receptors in the VMN has been considered to be deficient in castrated males [11, 23, 24] as compared to females, but the fact remains that estrogens are capable of inducing some accumulation of brain P receptors in castrated male hamsters [20] and rats [21, 22].

The literature to our knowledge contains only one report [21] of estrogen induction of P receptors in the hypothalamus of gonadally

intact male rodents. The present study was thus undertaken, firstly to determine the effects of estrogen treatment on P receptors in the MBH, and secondly to determine the influence of any changes in the population of hypothalamic P receptors on lordosis behavior in gonadally intact male rats.

MATERIALS AND METHODS

Animals

Adult male Wistar rats raised in our colony (strain WI) were used when 3 to 4 months old. They were kept under a reversed light–dark schedule (dark period: 15.00–01.00 h) and controlled conditions of temperature (22–24°C). They had free access to a commercial laboratory food (U.A.R.) and tap water *ad libitum*.

Experimental design

A first group of gonadally intact male rats was used to determine whether the effects of successive doses of estradiol benzoate (EB) on the display of lordosis behavior were dependent, as previously shown in castrated animals [15], on the dose of estrogen administered, and/or the level of P receptors in the MBH. Fifty three sexually inexperienced males were divided into two subgroups of 30 and 23 animals which received 1.0 and 2.5 μg EB, respectively (s.c.) dissolved in 0.1 ml olive oil every day at 08.00 h for 6 days. On the afternoon following the last EB injection, all the animals were tested for lordosis behavior. One month later the two subgroups were again given EB under the same temporal schedule of hormone treatment. However they were not tested for lordosis behavior so as to eliminate the well known stress related effects on the secretion of adrenocortical P [25] which result from the presentation of estrogen primed male rats to stimulus males. On the last day of EB injection, they were killed by decapitation at 15.00–17.00 h. Trunk blood was collected for P measurement and stored at −20°C until further use and brains were removed for P receptor assay in the MBH. In the animals given 1 μg EB, two pools of MBH were constituted for the animals that had displayed (lordosis group) and 2 pools for those which had not displayed lordosis (no lordosis group) during their behavioral testing. In the animals given 2.5 μg EB, 3 pools of MBH were constituted for the lordosis group and 1 pool only for the no lordosis group.

A second group of 24 animals comprised gonadally intact male rats which were used in the absence of any hormonal treatment. Recent findings in our laboratory [26] showed that sexually inexperienced male rats raised in our colony rarely responded by lordosis posture to the mounts of stimulus males. In contrast, masculine copulatory experience with highly receptive females rendered some males capable of exhibiting lordosis behavior when mounted by stimulus males [27]. This enabled us to select, 1 month following testing for lordosis behavior in response to male mounts, 12 animals that had displayed such behavior (lordosis group) and 12 other ones that had not (no lordosis group). All these animals served as controls for the animals given E_2 treatment. They were killed by decapitation for blood P measurement and P receptor assay in the MBH. Three pools of MBH were constituted for the lordosis group and the no lordosis group, respectively.

Testing for lordosis behavior

Behavioral tests were conducted under a dim light in a plexiglas mating arena (66 cm dia) by presenting the experimental rats for 10 min to sexually adult stimulus males at the beginning of the dark period between 15.00 and 17.00 h. The stimulus males which were selected had been shown, (1) to be fully active when tested with highly receptive ovariectomized females primed with EB and P and (2) to mount male congeners with sufficient vigor. The stimulus males were placed in the arena 5 min before the initiation of testing. As in castrated male rats [28], the following paradigms were used in intact male rats for the evaluation of lordosis behavior, (1) the proportion of animals in a given group that displayed willingness to mate and therefore showed at least one lordosis in response to the mounts of the stimulus males; and (2) the lordosis quotient (LQ) defined as number of lordosis/number of mounts × 100 served as a measurement of the mating performance. A mean LQ was computed in each group of animals. As in females, lordosis consisted of concave back flexion, head and rump elevation and lateral tail deviation.

Progestin receptor assay

The rats were sacrificed by decapitation and the MBH area removed according to the procedure described by Luine *et al.* [29]. Progestin receptors were assayed according to the method of Samama and Aron [22]. Briefly, the MBH

Table 1. Display of lordosis behavior in gonadally intact adult male rats given EB

Treatment[a] (μg EB)	Proportion of animals displaying lordosis responses	Mean LQ ± SEM in animals displaying lordosis	Mean number ± SEM of mounts displayed by the stimulus males
1	14/30	32.2 ± 3.8	6.8 ± 0.4
2.5	16/23[b]	47.5 ± 4.2[c]	8.1 ± 0.7[c]

[a]All animals were given EB daily at 08.00 h for 6 days. Testing for lordosis behavior was performed at the beginning of the dark period on the afternoon of the last injection.
[b]vs 1 μg EB; $P < 0.05$ (one tailed test).
[c]NS, not significant.

were homogenized in a glass/teflon homogenizer at 4°C in 1 ml of TED buffer (10 mM Tris, 1.5 mM EDTA, 0.5 mM dithiothreitol, pH 7.4). Homogenates were centrifuged at 900 *g* for 15 min. Supernatants were removed and the pellets were resuspended in 1 ml of TED buffer and centrifuged again (900 *g*, 15 min). This procedure was repeated and the 3 supernatants were pooled and centrifuged for 30 min at 200,000 *g* to provide the cytosolic fractions.

The cell nuclei contained in the 900 *g* pellets were lyzed at 4°C in 1 ml of TKED buffer (10 mM Tris, 1.5 mM EDTA, 0.5 mM dithiothreitol, 0.6 M KCl, pH 8.5). After 20 min stirring, these suspensions were centrifuged for 15 min at 900 *g*. After 3 successive treatments with TKED, the last centrifugation was performed at 200,000 *g* for 30 min, to provide the nuclear fractions. The final pellets served for DNA determination after addition of 5% trichloracetic acid.

Cytosolic and nuclear fractions were incubated with [^{3}H]R5020 for 18 h at 0–4°C in the absence or presence of a 100 fold excess of unlabeled R5020 [30]. Bound and free steroids were separated by addition of a charcoal dextran suspension in TED buffer (10 mM Tris, 1.5 mM EDTA, pH 7.4). After centrifugation for 10 min at 900 *g*, the radioactivity of aliquots of the supernatant was counted. Specific binding was calculated as the difference between non-specific binding (in the presence of unlabeled steroid) and total binding (in the absence of unlabeled steroid).

Results were expressed as fmol of [^{3}H]R5020 specifically bound per mg of DNA.

Progesterone radioimmunoassay

P was estimated after hexane extraction by radioimmunoassay using an antibody specific for 11α-hydroxyprogesterone hemisuccinate–bovine serum albumin (RIA Kit Biomérieux). P measurement was made without column separation because previous assays [31] using Sephadex LH 20 microcolumns [32] had shown that P values did not significantly differ using either procedure. Intraassay and interassay variation coefficients were 12 and 10%, respectively. The determinations were made in duplicate and plasma concentrations were expressed in ng/ml.

Statistics

The proportions of animals displaying lordosis behavior were compared using the Chi Square method (Table 1). Numbers of P receptors and blood P values were analyzed after logarithmic transformation of the data. Two way analysis of variance for unequal numbers served to compare the numbers of P receptors in the MBH of EB injected animals (Table 2).

Table 2. Progesterone receptors in the MBH of gonadally intact male rats given or not EB

Treatment[a] (μg EB)	Total nuclear and cytosolic P receptors (fmol/mg DNA)[b]	Cytosolic P receptors (fmol/mg DNA)	Nuclear P receptors (fmol/mg DNA)
None			
Lordosis group (12)	264 ± 55[c]	167 ± 38	97 ± 21
No lordosis group (12)	236 ± 81	151 ± 60	85 ± 20
1			
Lordosis group (14)	384 ± 8[d]	231 ± 42	153 ± 35
No lordosis group (16)	270 ± 48	139 ± 20	131 ± 68
2.5			
Lordosis group (16)	494 ± 23[d,e]	292 ± 30	202 ± 7
No lordosis group (7)	401	235	165

The numbers of animals are in parentheses.
[a]Removal of MBH on the afternoon of the last day of injections. EB was given daily for 6 days.
[b]The values represent the mean (±SEM) of 2 to 3 assays with duplicate determination except for the no lordosis group given 2.5 μg EB, where only one assay was performed.
[c]vs no lordosis; NS, not significant.
[d]vs no lordosis; $P < 0.05$.
[e]vs 1 μg EB and no EB; $P < 0.05$.

Table 3. Blood progesterone concentration in gonadally intact adult male rats given or not given EB daily at 08.00 h for 6 successive days

Treatment[a] (μg EB)	Progesterone ng/ml ± SEM	
	Lordosis group	No lordosis group
No	1.180 ± 0.200[b] (12)	0.670 ± 0.070 (12)
1	1.282 ± 0.240[c] (14)	1.722 ± 0.147 (16)
2.5	0.603 ± 0.127[c,d] (16)	1.611 ± 0.411[d] (7)

The numbers of animals are in parentheses.
[a]Blood collected by decapitation at 15.00–17.00 h on the afternoon of the last injection.
[b]Lordosis vs no lordosis group; $P < 0.025$.
[c]Lordosis vs no lordosis group; $P < 0.05$.
[d]2.5 vs 1 μg; $P < 0.01$.

Analysis of variance for parallel line assays was used for the statistical evaluation of dose related effects of EB on the number of P receptors in the MBH (Table 2). Blood P values (Table 3) were compared either by two way analysis of variance for unequal numbers (EB injected animals) or by one way analysis of variance (no EB).

RESULTS

Table 1 shows that male rats which were given 2.5 μg EB daily for 6 days displayed lordosis responses more frequently to male mounts than those which received 1 μg EB under the same temporal schedule of hormone treatment ($P < 0.05$, one tailed test).

As shown in Table 2, the number of P receptors in the MBH of the animals which were not given EB did not differ between the lordosis and the no lordosis groups (264 vs 236 fmol/mg DNA, respectively). In the animals given EB, the total number of nuclear and cytosolic P receptors appeared to be higher in the lordosis group than in the no lordosis group ($F^1_4 = 9.07$; $P < 0.05$). A significant increase in the number of P receptors in the MBH was also observed, in both the lordosis and the no lordosis group, in the animals given 2.5 μg EB as compared to those given 1.0 μg EB and those which were not given EB (494, 384, 264 fmol/mg DNA and 401, 270, 236 fmol/mg DNA, respectively) (linear regression; $F^1_8 = 6.82$; $P < 0.05$, deviation of linearity; $F^1_8 = 0.06$, NS; deviation of parallelism: $F^1_8 = 0.01$; NS).

The results presented in Table 3 indicate that in the absence of EB treatment blood P values were greater in the lordosis than in the no lordosis group ($F^1_{22} = 5.52$; $P < 0.05$). Following EB treatment P values in the no lordosis group significantly exceeded those observed in the lordosis group ($F^1_{49} = 6.35$; $P < 0.025$). A statistically significant decrease in blood P values was noted in the animals given 2.5 μg as compared to those receiving 1.0 μg EB ($F^1_{49} = 11.44$; $P < 0.01$).

DISCUSSION

The present results provide evidence that doses of estrogen which activated lordosis behavior in sexually inexperienced gonadally intact male rats were effective in elevating P receptor levels in the MBH in a dose dependent manner. The animals given 2.5 μg EB displayed more frequent lordosis behavior (lordosis group) in response to male mounts than those given 1.0 μg EB, an effect which paralleled the rise in the number of MBH P receptors. On the other hand, P receptors in the MBH were less numerous in EB treated animals showing no lordosis responses (no lordosis group) than in those of the lordosis group. We did not measure hypothalamic P receptors in the cyclic female rats bred in our colony because it was not within the scope of our work. However, it is worth mentioning that the number of EB induced P receptors in the MBH of the Wistar males used in this study largely exceeded that of P receptors present in the hypothalamus of cyclic female rats at a stage of proestrus immediately preceding behavioral estrus [33].

The question must then be raised why the effects of EB priming are generally thought to be less marked in castrated males than in castrated females [11, 21, 23, 24, 34]. It may be that castrated animals are less sensitive to estrogens than gonadally intact animals. It is known [3, 4, 16] that lordosis patterns may be more successfully induced by estrogens in intact than in castrated males. Alternatively, perhaps a strain difference in response to estrogens exists. Most of the results reported in castrated animals were obtained in Sprague–Dawley rats, while our own experiments and those of Van de Poll and Van Dis [3] were conducted in Wistar rats. Moreover, in the Wistar rats raised in our colony, the males of the WII strain appeared more responsive to estrogens than did those of the WI strain [4].

A second point deserves attention. In the absence of any hormonal treatment, a low concentration of hypothalamic P receptors has been found in castrated male rats [21, 22, 34] and hamsters [20]. Thus far, information is poor concerning the level of hypothalamic P receptors in gonadally intact male rats in the

absence of estrogen treatment. Moguilewsky and Raynaud [21] detected more P receptors in intact than in castrated animals. Our own results are consistent with these data. Previously we reported [22] that the MBH of castrated WI male rats contained a small number of P receptors (14 ± 2 fmol/mg DNA). In the present work we found 236 ± 55 and 264 ± 81 fmol/mg DNA in the hypothalamus of the gonadally intact animals of the no lordosis and lordosis groups, respectively. It is thus tempting to assume that some yet unknown hormonal mechanisms operating in intact animals are responsible for the increase in the number of constitutively expressed P receptors present in the hypothalamus as compared to castrated males.

The hormonal mechanisms which subserve the induction of lordosis behavior by estrogens in the male rat are different in gonadally intact and castrated animals. In castrated male rats primed with successive doses of estrogen, EB was shown to increase adrenocortical P secretion in a dose dependent manner [15] and this rise in endogenous P appeared to facilitate the induction of lordosis behavior by estrogen. In contrast, in gonadally intact male rats submitted to the same schedule of EB treatment, the display of lordosis behavior was negatively correlated with the blood P concentration. Moreover the animals of the lordosis group showed significantly lower P values than those of the no lordosis group. It is therefore likely that in the present experimental model some estrogen induced feed-back mechanisms controlling adrenocortical P secretion at the hypothalamus–pituitary level operate differently in castrated and gonadally intact animals and more efficiently in the males showing lordosis than in those which did not. Indeed further experiments are necessary to clarify this problem. In any case, the present findings clearly demonstrate that estrogens are able to induce accumulation of MBH P receptors in gonadally intact male rats, as they do in female rats [35] and in female guinea pigs [36].

In the absence of EB treatment, we did not find more MBH P receptors in the animals of the lordosis than in those of the no lordosis group. On the other hand, blood P levels were higher in the lordosis than in the no lordosis group as previously described by Schaeffer *et al.* [27]. It is well known [28] that olfactory cues originating from the male are capable of facilitating the display of lordosis behavior in male rats castrated in adulthood and primed with EB + P and that the perception of olfactory cues is strictly dependent on P [4]. An increase in P receptors in the MBH has also been observed in castrated male rats primed with EB. Therefore we could have expected higher MBH P receptor concentrations in the lordosis than in the no lordosis group. However it is worth noting that the animals were sacrificed one month after their last test for lordosis behavior. Hence the possibility can not be ruled out that the hormonal conditions and the environmental stimulus necessary for an increase of the hypothalamic P receptors were not present at the time of death.

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