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# Reproductive Behavioral Responsiveness to Noradrenergic Stimulation in Developing Guinea Pigs

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OLSTER, D. H. *Reproductive behavioral responsiveness to noradrenergic stimulation in developing guinea pigs*. PHARMACOL BIOCHEM BEHAV **59**(3) 551–556, 1998.—The stimulatory effects of ovarian hormones on sexual receptivity in guinea pigs may be mediated by norepinephrine. Juvenile females rarely exhibit steroid-induced receptivity and also respond poorly to the lordosis-enhancing action of α-noradrenergic receptor stimulation. This experiment was designed to chart the development of behavioral responsiveness to the α-noradrenergic agonist, clonidine, and to test the hypothesis that higher doses of estradiol and/or clonidine are required to stimulate lordosis in juvenile compared to adult guinea pigs. Ovariectomized females received estradiol benzoate (10 μg or 50 μg SC) 40–48 h before administration of clonidine (1 mg/kg or 5 mg/kg IP) or saline at 14–17-day intervals. Regardless of treatment, few animals (0–36%) displayed lordosis at 20, 34, or 48 days of age. At 65 days of age, in both estradiol dose groups significantly more clonidine- (1 mg/kg) than saline-injected animals displayed lordosis (80–91 vs. 0–33%, respectively). Clonidine (5 mg/kg) was ineffective at all ages. These data do not support the hypothesis that behavioral responsiveness to α-noradrenergic receptor stimulation in immature females can be elicited by increasing the doses of estradiol and/or clonidine. These results suggest the occurrence of a maturational change in the neural systems governing noradrenergic involvement in steroid-induced sexual behavior in guinea pigs. © 1998 Elsevier Science Inc.

Lordosis Sexual behavior Puberty Estradiol Noradrenergic

IN adult female rats and guinea pigs, the display of sexual receptivity around the time of ovulation is dependent upon the release of ovarian steroid hormones. Ovariectomized (OVX) females do not exhibit lordosis, but the behavior is reliably restored after replacement with estradiol or subthreshold doses of estradiol followed by progesterone (5,6,12,44). A number of observations suggest that the inductive effects of ovarian hormones on sexual receptivity in rats and guinea pigs are mediated, at least in part, by activation of the central noradrenergic system (13,24). In OVX guinea pigs, for example, pharmacological inhibition of norepinephrine biosynthesis or administration of noradrenergic receptor antagonists severely attenuate the behavioral response to estradiol and progesterone (24,25). Conversely, administration of noradrenergic agonists to estradiol-primed, OVX females stimulates the display of lordosis (7,8). The effectiveness of drugs such as clonidine to stimulate lordosis, and phenoxybenzamine to inhibit the behavior, suggest that α-receptor subtypes mediate these actions of noradrenergic manipulation on sexual receptivity.

In contrast to what is observed in adults, OVX juvenile guinea pigs do not respond behaviorally to ovarian hormones (14,33,47). In this laboratory, OVX Hartley guinea pigs do not display adult-typical lordosis responses to estradiol and progesterone until 40–50 days of age (29,30). Because neonatal guinea pigs display steroid-independent lordosis responses to anogenital licking by their dams for approximately 8 h after birth, it is clear that these animals are capable of generating the posture at a very young age (3). The absence of steroid-induced lordosis in immature guinea pigs is in marked contrast to rats, in which steroid hormones facilitate the display of lordosis during the neonatal period (45,46).

The mechanisms underlying immature guinea pigs' behavioral hyporesponsiveness to ovarian steroid hormones are not entirely clear, but may include deficiencies in estrogen and progestin receptor populations in key hypothalamic regions (27,29,31,34), existence of an overriding inhibitory system that prevents the display of lordosis (26,28,32), and insensitivity to the facilitatory action of α-noradrenergic receptor stimulation

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on sexual receptivity. Whereas estradiol-primed, OVX adult guinea pigs readily display lordosis in response to administration of the α-noradrenergic receptor agonist, clonidine (7,8), preliminary data obtained in a small group of animals indicate that immature females do not (30).

This study was designed to explore the development of reproductive behavioral responsiveness to α-noradrenergic receptor stimulation in female guinea pigs and to test the hypothesis that juvenile females require higher doses of estradiol and/or clonidine than adults to demonstrate a stimulation of lordosis by α-noradrenergic receptor stimulation. All that has been reported in terms of a dose–response relationship between clonidine and the induction of lordosis in estradiol-treated OVX guinea pigs is that IP administration of 0.1 mg/kg or 0.5 mg/kg of the drug is not effective, whereas injection of 1.0 mg/kg both induces lordosis in animals not showing the behavior and prolongs its display in animals exhibiting estrogen heats (8). Interestingly, in OVX adults receiving both estradiol and progesterone, 0.5 mg/kg clonidine (IP) does facilitate sexual receptivity (7). Thus, it may be true that females near or at a threshold for displaying lordosis may require less clonidine to facilitate the behavior than females that are not. If this is the case, perhaps higher doses of clonidine (>1.0 mg/kg) would be effective in eliciting lordosis in developing females.

## METHOD

Twenty-three Hartley female guinea pigs (10 days old upon arrival) were purchased from Charles River Laboratories (Wilmington, MA). They were housed in pairs in plastic tubs (17.5 in. L × 10 in. W × 8.5 in. H) until 39 days of age, at which time they were transferred to stainless steel cages (six females/cage; 36 in. L × 24 in. W × 15 in. H). The animal room was maintained on a 12 L:12 D photoperiod, with lights on from 0700 to 1900 PST. Throughout the study, food (Guinea Pig Diet #5025, PMI Feeds, Inc., St. Louis, MO) and water were available ad lib. At 12–13 days of age all of the animals were OVX via bilateral dorsal incisions under anesthesia induced by the inhalant, Metofane (methoxyflurane), and Innovar-vet (0.02 ml/animal IM). Both drugs were purchased from Pittman-Moore (Washington Crossing, NJ).

Each animal was randomly assigned to a high or low dose estradiol group for the entire study. At 20, 34, 48, and 65 days of age each estradiol-treated female was tested for the display of sexual receptivity following administration of clonidine (two different doses) or vehicle, according to the following protocol: each OVX female was primed with a SC injection of 10 or 50 μg estradiol benzoate (EB, dissolved in sesame oil, Sigma Chemical Co., St. Louis, MO; n = 11–12/group). At 0800 h on the day of behavioral testing (i.e., 40 h after injection of EB), each female received clonidine (1 mg/kg or 5 mg/kg IP of clonidine HCl, pH 7.5, Sigma) or the 0.9% saline vehicle and was tested for the display of sexual behavior as described below. All injections were in a volume of 0.5 ml/kg. The second round of clonidine/saline injections and lordosis testing began after all animals had stopped showing lordosis in the first round, and the third set of injections and testing followed the second set of trials. At least 4 h elapsed between rounds of clonidine/saline injections. Each female received the saline and clonidine injections in a counterbalanced order, both within and across behavioral testing days.

The animals were tested for lordosis by manual palpation in their home cages as described previously (48), with the experimenter blind to the treatment groups. Any female displaying lordosis before the first clonidine/saline injection (i.e., in response to EB alone) was eliminated from the experiment for that day. Behavioral testing began 30 min after clonidine or saline injection, and was repeated at 30 min intervals for 3 h, and then at hourly intervals, until all animals did not show lordosis on two consecutive hourly tests. The criterion for a positive response was the display of lordosis for at least 2 s on two consecutive tests. The data collected included percentage of females displaying lordosis, and in positive responders, the latency to lordosis (from clonidine/saline injection), maximum lordosis duration (the maximum length of time an animal held the posture on any test), and heat duration.

The percentage of females responding to clonidine compared to saline injection at each age was analyzed by the binomial test (35). The latency to lordosis, maximum lordosis duration and heat duration in positive responders were not compared among clonidine and saline treatment groups due to the low number of responders in the high dose clonidine and saline-injected groups. However, these measures in high and low EB dose groups receiving 1 mg/kg clonidine at 65 days of age were compared by Student's t-test. In all cases a $p$ value $< 0.05$ was the criterion for statistical significance.

## RESULTS

These OVX guinea pigs rarely displayed lordosis 40 h after injection of EB at any age. Of the 23 animals tested at four different ages only 1 female primed with 50 μg EB displayed lordosis prior to any drug or saline injection, and this occurred at 65 days of age. Furthermore, regardless of EB priming dose, there was no significant difference in the percentage of females displaying sexual receptivity following injection of either dose of clonidine (1 mg/kg or 5 mg/kg) compared to the saline vehicle at 20, 34, and 48 days of age (Tables 1 and 2). At most, 25% of saline-injected females responded, compared to a maximum of 36% of clonidine-treated animals. The behavioral responses to saline tended to be sporadic. It was not always the same animals responding to saline at the different ages; nor was it true that the few animals displaying lordosis following clonidine injections at these first three time points were always the same as those responding to saline. However, it was the case that if an animal displayed lordosis following injection of 1 mg/kg clonidine at an age prior to 65 days, it always responded to this treatment at subsequent ages. The only other noticeable behavioral responses to the clonidine injections were piloerection and mild sedation, which tended to occur 30 and 60 min following the drug injection at all ages.

It was not until 65 days of age that an overall significant response to clonidine (vs. saline) was observed in either EB dose group. At this age 80–91% of females receiving 1 mg/kg clonidine became sexually receptive compared to 0–33% following saline injection. The 5 mg/kg dose of clonidine, in contrast, did not stimulate the display of lordosis in either EB dose group at this age. The characteristics of the lordosis responses are also shown in Tables 1 and 2. When it was effective, animals began displaying lordosis to clonidine 60–90 min after the injection. As has been reported previously (8), the lordosis observed was a definite flattening of the back, but weaker than the more typical, pronounced arch observed in response to estradiol and progesterone replacement in OVX adults. The sexual receptivity was occasionally accompanied by rumbling vocalizations. In both EB dose groups animals continued to display lordosis for 1–2 h after the clonidine injection and then became unreceptive. There were no significant differences between the two EB dose groups in the latency to lordosis [relative to clonidine injection; $t(16) = -1.9$,

TABLE 1

LORDOSIS RESPONSES IN OVX GUINEA PIGS FOLLOWING INJECTION OF ESTRADIOL BENZOATE (10 μg) AND CLONIDINE (1 OR 5 mg/kg) OR THE 0.9% SALINE VEHICLE (POSITIVE RESPONDERS ONLY; ALL DATA ARE MEAN ± SEM)

| | Number of Responders | Latency to Lordosis (h) | Maximum Lordosis Duration(s) | Heat Duration (h) |
|---|---|---|---|---|
| 20 days of age | | | | |
| 0.9% saline | 1/12 | 1.5 | 5.0 | 1.0 |
| 1 mg/kg clonidine | 0/12 | — | — | — |
| 5 mg/kg clonidine | 1/12 | 1.5 | 7.0 | 1.0 |
| 34 days of age | | | | |
| 0.9 % saline | 2/12 | 1.2 ± 0.4 | 4.3 ± 0.9 | 1.2 ± 0.2 |
| 1 mg/kg clonidine | 2/12 | 0.8 ± 0.3 | 4.0 ± 0 | 1.8 ± 0.3 |
| 5 mg/kg clonidine | 0/12 | — | — | — |
| 48 days of age | | | | |
| 0.9% saline | 2/12 | 1.8 ± 0.3 | 4.5 ± 0.5 | 1.0 ± 0 |
| 1 mg/kg clonidine | 3/12 | 1.2 ± 0.3 | 6.0 ± 0.5 | 1.5 ± 0.3 |
| 5 mg/kg clonidine | 2/12 | 1.3 ± 0.3 | 5.5 ± 1.5 | 1.0 ± 0 |
| 65 days of age | | | | |
| 0.9% saline | 4/12 | 1.3 ± 0.1 | 3.8 ± 0.6 | 1.5 ± 0.3 |
| 1 mg/kg clonidine | 11/12* | 1.4 ± 0.2 | 3.5 ± 0.3 | 1.3 ± 0.1 |
| 5 mg/kg clonidine | 1/12 | 0.5 | 6.0 | 1.5 |

*$p < 0.05$ vs. response to saline at that age.

$p > 0.05$], maximum lordosis duration, [$t(16) = 0.5$, $p > 0.05$], or heat duration [$t(16) = -1.9$, $p > 0.05$] following injection of 1 mg/kg clonidine at 65 days of age.

## DISCUSSION

These data confirm previous observations that juvenile (~3-week-old) female guinea pigs, when OVX and primed with 10 μg EB, do not exhibit an enhancement of lordosis in response to injection of the α-noradrenergic receptor agonist, clonidine [1 mg/kg, (30)]. This is a standard, effective combination of estradiol and clonidine that facilitates the display of lordosis in OVX adult guinea pigs (8,24,30). This study extends that observation with the demonstration that behavioral responsiveness to clonidine develops between 48 and 65 days of age. The robust response to clonidine appears at an age near—or perhaps slightly later than—that when females show adult-typical behavioral responsiveness to estradiol and progesterone [40–50 days of age (29,30)], and well after vaginal opening and the natural onset of ovarian cyclicity [~4 weeks of age for Hartley females in this laboratory (32)]. These data suggest that a maturational process occurs during which developing guinea pigs become responsive to the combination of estradiol and clonidine. If α-noradrenergic receptor stimulation mediates, in part, the behavioral effects of ovarian steroid hormones on sexual receptivity in this species, the lack of sensitivity to a noradrenergic stimulus prior to 65 days of age may contribute to immature females' behavioral hyporesponsiveness to estradiol and progesterone.

Furthermore, and in opposition to the proposed hypothesis, higher doses of EB or clonidine were not effective at earlier ages. This observation suggests that the hyporesponsiveness of juvenile guinea pigs to clonidine is not simply due to inadequate estradiol priming that could be overcome by administration of a higher dose of estradiol. The lack of behavioral responsiveness to the 5.0 mg/kg dose of clonidine may reflect the hypotensive (1,16) and/or sedative actions (9,10,17) of the drug, which might prevent guinea pigs from showing lordosis at this dose. However, no obvious behavioral differences (e.g., degree of sedation) were observed in the animals receiving the two different clonidine doses. Furthermore, when clonidine was effective, the display of lordosis continued after the sedative effects had abated. Alternatively, the U-shaped dose–response curve may also reflect action of higher doses of clonidine at multiple receptor subtypes, both pre- and postsynaptic (1,15,21,36), in systems that might interfere with the display of lordosis.

The mechanism by which clonidine enhances lordosis in adult guinea pigs has not been elucidated, but it does seem to be mediated by postsynaptic, rather than presynaptic noradrenergic receptors. The reduction in the display of progesterone-facilitated lordosis observed following treatment with an inhibitor of dopamine-β-hydroxylase is reversed by administration of clonidine (24). It is unlikely that activation by clonidine of presynaptic noradrenergic receptors (that would presumably lower noradrenergic transmission even more) would reverse the effects of the dopamine-β-hydroxylase inhibitor. As to determination of the noradrenergic receptor subtype involved in steroid-induced lordosis in adult guinea pigs, administration of an $\alpha_1$-receptor agonist (methoxamine or phenylephrine) does not facilitate the display of lordosis in estradiol-treated, OVX adults (41,43). Injection of an $\alpha_2$-receptor agonist does enhance sexual receptivity in this model, and $\alpha_1$-receptor stimulation can facilitate the lordosis response to subthreshold doses of $\alpha_2$-receptor agonists (41). The lordosis-enhancing actions of clonidine in estradiol-primed, OVX guinea pigs are attenuated by injection of $\alpha_1$-[prazosin (25)] or $\alpha_2$-noradrenergic receptor antagonists [yohimbine and idozoxan (43)], suggesting the involvement of both α-receptor subtypes in the clonidine response.

One possible explanation for the behavioral hyporesponsiveness of juvenile female guinea pigs to clonidine is that

TABLE 2

LORDOSIS RESPONSES IN OVX GUINEA PIGS FOLLOWING INJECTION OF ESTRADIOL BENZOATE (50 μg) AND CLONIDINE (1 OR 5 mg/kg) OR THE 0.9% SALINE VEHICLE (POSITIVE RESPONDERS ONLY; ALL DATA ARE MEAN ± SEM)

| | Number of Responders | Latency to Lordosis (h) | Maximum Lordosis Duration(s) | Heat Duration (h) |
|---|---|---|---|---|
| 20 days of age | | | | |
| 0.9% saline | 1/11 | 0.5 | 17 | 1.0 |
| 1 mg/kg clonidine | 0/11 | — | — | — |
| 5 mg/kg clonidine | 0/11 | — | — | — |
| 34 days of age | | | | |
| 0.9% saline | 1/11 | 0.5 | 7.0 | 1.5 |
| 1 mg/kg clonidine | 0/11 | — | — | — |
| 5 mg/kg clonidine | 1/11 | 1.0 | 4.0 | 1.5 |
| 48 days of age | | | | |
| 0.9% saline | 1/11 | 1.5 | 4.0 | 1.0 |
| 1 mg/kg clonidine | 4/11 | 1.0 ± 0.3 | 7.7 ± 3.2 | 1.5 ± 0.3 |
| 5 mg/kg clonidine | 3/11 | 2.2 ± 0.4 | 7.0 ± 3.0 | 1.2 ± 0.2 |
| 65 days of age | | | | |
| 0.9% saline | 0/10 | — | — | — |
| 1 mg/kg clonidine | 8/10* | 1.2 ± 0.2 | 5.6 ± 1.2 | 1.5 ± 0.2 |
| 5 mg/kg clonidine | 1/10 | 0.5 | 7.0 | 2.0 |

*$p < 0.05$ vs. response to saline at that age.

the relevant noradrenergic receptor populations are not adequately developed until after 48 days of age. The mediobasal hypothalamus (and not the medial preoptic area) is one site at which clonidine injection results in a facilitation of lordosis in estradiol-primed, OVX adults (22). Concentrations of $\alpha_1$-noradrenergic receptors (as measured by *in vitro* radioligand binding assay) have been reported to be higher in the hypothalamus of ovary-intact neonatal compared to 60-day-old OVX guinea pigs, with no differences found at intermediate ages (20). While these data provide no evidence for inadequate concentrations of $\alpha_1$-noradrenergic receptors in juvenile females, homogenization of whole hypothalamus precludes detection of age-related differences in more discrete brain regions. Furthermore, the fact that only the adults were OVX (all other age groups were ovary intact) confounds the interpretation because estradiol influences both noradrenergic activity (2,13) and $\alpha_1$-noradrenergic receptor binding in the central nervous system (18,19).

One of the goals of this study was to test the hypothesis that increasing the priming dose of estradiol would instill behavioral responsiveness to the drug in juvenile guinea pigs. This hypothesis was not supported by the data. It has not been determined whether estradiol priming is critical for the display of behavioral responsiveness to clonidine in guinea pigs. Evidence against this notion comes from the observation that injection of the α-noradrenergic antagonist, prazosin, blocks hormone-induced lordosis in OVX adult strain 2 guinea pigs, and steroid-independent lordosis exhibited by castrated males of this strain (38). The differential dependence on ovarian steroid hormones for the display of lordosis precludes assuming that identical mechanisms underlie the interaction between steroid hormones and noradrenergic systems in the two strains. One proposed mechanism by which α-noradrenergic antagonists attenuate progesterone-facilitated lordosis is a reduction in the concentration of hypothalamic cytosol progestin receptors, an effect that is observed only if the OVX females are pretreated with estradiol (23,25). This may indicate that noradrenergic effects on sexual receptivity depend on estradiol exposure in guinea pigs. Moreover, in rats, a combination of ovarian steroid hormone priming and sensory stimulation is required to observe stimulus-induced release of norepinephrine in the ventromedial nucleus of the hypothalamus (13). If estradiol priming is necessary, then inadequate responsiveness to estradiol may underlie the behavioral hyporesponsiveness of juvenile guinea pigs to clonidine. Consistent with this notion is previous work from this laboratory documenting fewer estrogen receptor-immunoreactive cells in the ventrolateral hypothalamus of juvenile compared to adult guinea pigs (27). This region of the brain is a site at which estradiol implantation effectively primes OVX adult guinea pigs for behavioral responsiveness to subsequent progesterone administration (11). This brain area also receives noradrenergic projections, which may modulate estrogen-responsive neurons (37). Thus, it is conceivable that an estrogen receptor deficiency in this region prevents an adequate priming action of estradiol that may be required for sensitivity to clonidine.

In OVX adult guinea pigs, administration of α-noradrenergic receptor antagonists inhibit the display of progesterone-facilitated lordosis (24). Investigators have questioned whether the noradrenergic system is mediating progesterone action in estradiol-primed animals, and whether clonidine is mimicking the actions of progesterone or influencing progestin receptor action. As mentioned above, one mechanism proposed to account for the inhibition of progesterone-facilitated lordosis by α-noradrenergic receptor blockade is a reduction in the concentration of hypothalamic estradiol-induced cytosol progestin receptors. This effect is specific to the ventromedial nucleus and/or arcuate nucleus/median eminence (39,42). However, this decrease in hypothalamic cytosol progestin receptors appears to be accompanied by an increase in cell nuclear progestin receptor accumulation, suggesting that the mechanism by which α-noradrenergic blockers decrease sexual be-

havior is not due to disruption of the progestin receptor system (4). The fact that clonidine facilitation of lordosis in estradiol-primed OVX adults is not attenuated by treatment with the progestin receptor antagonist, RU 486, is in agreement with this thesis (40). Finally, the lordosis induced by clonidine in estradiol-primed animals differs from that observed in response to progesterone in several respects, including a much shorter latency (1–1.5 h vs. an average of 4 h after progesterone), duration (1–2 h, compared to 4–8 hours for progesterone), and the actual physical characteristics of the response (29,30). Thus clonidine is not simply mimicking the actions of progesterone.

In summary, juvenile guinea pigs are relatively slow to develop behavioral responsiveness to the lordosis-enhancing action of the α-noradrenergic receptor agonist, clonidine. The adult-typical behavioral response cannot be elicited by administration of higher priming doses or estradiol, nor by the use of higher doses of clonidine. These data are consistent with the hypothesis that behavioral hyporesponsiveness to estradiol and progesterone in immature guinea pigs may be due, at least in part, to the inability to respond to a noradrenergic signal mediating the stimulatory effects of ovarian steroid hormones on reproductive behavior.

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