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The Influence of α-Receptors on Lordosis in the Female Rat

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DAVIS, G. A. AND R. KOHL. *The influence of α-receptors on lordosis in the female rat.* PHARMAC. BIOCHEM. BEHAV. 6(1) 47–53, 1977. — The α-adrenergic agonist clonidine suppressed lordotic responding in spayed female rats brought into heat by estrogen and progesterone. The suppression was blocked by the α-antagonist yohimbine, but not by phenoxybenzamine or pimozide. Phenoxybenzamine itself had no suppressive effect on lordosis, though yohimbine did under some conditions. These results argue against an important facilitatory influence of norepinephrine on lordosis in the rat. Further, in comparison with the quite different findings recently reported from the guinea pig, they offer support for the presence of two different kinds of α-adrenergic receptors in the brain with different physiological functions.

Clonidine Norepinephrine Phenoxybenzamine Pimozide Sexual behavior Yohimbine

IN THE past several years, evidence has accumulated that a number of neurotransmitters in the brain can influence the display of lordosis in female rats [13,43]. For most transmitters, including serotonin, dopamine and acetylcholine, this influence appears to be a negative one. Elevation of transmitter levels or stimulation of receptors supresses lordotic responding, while interference with the synaptic action of the transmitter can lead to facilitation of responding, even in the absence of progesterone. Recently, however, evidence has been reported that norepinephrine (NE) may have a positive effect on lordosis, both in rat [13] and in guinea pig [6]. The strongest support for this idea is from the findings in the latter species that clonidine, an α-adrenergic agonist, increased the duration of the lordotic response, while the α-adrenergic antagonist, phenoxybenzamine, completely blocked responding. In similar experiments with rats, however, we made some unexpected findings: clonidine suppressed responding, while phenoxybenzamine had no effect. In this paper we report these results and attempt to understand the discrepancies between the two species in terms of two different kinds of α-adrenergic receptors.

The evidence is now substantial for at least two kinds of α-adrenergic receptor in the brain which have quite different physiological functions and which can be differentiated by their response to various α-adrenergic antagonists (see Discussion). Phenoxybenzamine, for instance, is highly effective against one kind of receptor, arbitrarily called α_2, and not against the α_1 receptor, while another drug, yohimbine, has the opposite specificity. Consequently we were interested to determine through use of these two drugs whether the suppression of lordosis in the rat by clonidine is mediated through α_1 or α_2 receptors. The results of these experiments, in comparison with reported findings in guinea pig [6], provide additional support for two kinds of α-adrenergic receptors and imply that they are differently distributed among the two rodent species in their influence on lordosis behavior. The results further argue that NE in the rat, unlike the guinea pig, does not have an important facilitatory role in the control of lordosis.

METHOD

Animals

Female rats from Holtzman (around 250 g) were bilaterally ovariectomized, then given estradiol benzoate (EB) (10 μg) followed 48 hr later by progesterone (P) (1 mg). One group of animals was obtained from Sprague-Dawley and treated similarly. All animals were housed in pairs under a lighting cycle of 14 hr light and 10 hr dark.

Behavioral Testing

For testing, the vagina of the female was covered with a piece of adhesive tape in order to minimize the occurrence of intromissions, which can lead to deficits in receptivity [19]. She was then placed for a period of 5 min in a glass fish tank (30 × 33 × 60 cm) with two vigorous males adapted to the tank. The males generally mounted 7–10 times in this period and were replaced as necessary to maintain this rate. They were also allowed occasional intromissions with a separate set of highly receptive females in order to maintain their sexual interest. The responses of the test females were expressed as a lordosis quotient (LQ), which is the lordisis-to mount ratio times 100.

Some other measures of receptivity were also taken. The intensity of lordosis (degree of curvature) was estimated on a 1–3 scale [19]. The female acceptance ratio was defined as the ratio of accepted mounts to total mount attempts. A

mount was scored as rejected if the female lifted a rear leg or turned over on her back. In some experiments the average duration of the lordotic responses was determined with a cumulative stopwatch, and individual responses exceeding 1.5 sec were also noted down. Statistical comparisons for all data were made with the Mann-Whitney U-test.

General Injection and Testing Paradigm

The particular experimental paradigms are described precisely for each experiment in the Results section. All animals were first primed with EB (2 μg/kg/ day, SC in 0.1 ml corn oil) for 5 days then tested on the fifth day before and after injection of P and/or various drugs. The average LQ in animals after estrogen alone was generally less than 15, and any animal with an LQ over 20 was not used further. All testing after P or drugs was done 2–6 hr after the beginning of the dark phase of the cycle.

In the first few experiments (Table 1) estrogen primed animals were given drugs without any P treatment. In all other experiments the primed rats were first given P (2 mg/ml in 0.1 ml corn oil, SC) and tested 4–6 hr later. Some of these animals then received clonidine while others were given an antagonist drug followed by clonidine. At least two weeks intervened between experiments, and several of the most important findings were repeated on fresh animals not given any drugs previously (as indicated under Results). Animals receiving phenoxybenzamine were not used again.

Drugs

All drug injections were intraperitoneal except for phenoxybenzamine which was given subcutaneously. Clonidine HCl (Boehringer) was injected in 1.0 ml/kg saline, while yohimbine HCl (Sigma) was dissolved at 1 mg/ml in saline and different volumes injected depending on the dose required. Pimozide (Janssen) was dissolved in a few drops of glacial acetic acid, then diluted with water to 1 mg/ml and adjusted to a pH of about 4 with sodium hydroxide. The dose given the rats was 1 mg/kg. Phenoxybenzamine (Smith Kline and French) was dissolved in 50% propylene glycol and injected at a dose of 20 mg/kg in 1.0 ml/kg.

RESULTS

Effects of Clonidine and Pimozide on Sexual Receptivity of Ovariectomized, EB Primed Rats

Since amphetamine has been reported to facilitate lordosis in the absence of P, possibly through a noradrenergic action [13], the α-adrenergic agonist clonidine was given to EB primed rats to determine if it might have a similar effect. Two fairly high doses, however, were completely ineffective (Table 1). When given together with pimozide, as amphetamine had been [13], clonidine blocked rather than facilitated the lordosis produced by pimozide (Table 1). The two higher doses of clonidine used, 125 and 400 μg/kg, produced substantial sedation in the animals, but the lower dose, 33 μg/kg, did not noticeably alter their behavior.

Effects of Injections with Clonidine and Other Drugs, Alone or in Combination, on the Lordosis Quotient of Rats Made Receptive with EB and P

Lordotic responding in animals treated with P was suppressed by clonidine (Tables 2, 3, 4). One hundred μg/kg was somewhat more effective than 33 μg/kg, but also gave rise to significant sedation. The degree of suppression did not vary from 0.5 to 1.5 hr after injection.

Yohimbine and several other α-adrenergic antagonists have been reported to reverse a number of the physiological effects of clonidine. Pretreatment at a dose of 2 mg/kg with this drug largely prevented the inhibitory action of clonidine on lordosis in animals treated with progesterone (Table 2), and this finding was replicated with a fresh group of animals which were tested 1 hr after the yohimbine injection as well as later after subsequent clonidine injection (Table 3). At a dose of 1 mg/kg, yohimbine was not significantly effective while at 5 mg/kg it appeared to reduce the LQ even below the level with clonidine alone. The animals receiving this high dose of yohimbine were noticeably debilitated, even before the clonidine was given. In lower doses, 1 mg/kg and 2 mg/kg, yohimbine by itself, in experiments with Holtzman animals, had no obvious effect on behavior and did not disturb the lordotic responding induce by P (Table 3). However, when two separate batches of animals obtained from Sprague-Dawley were tested with 2 mg/kg yohimbine after P treatment, the LQ was substantially reduced (Table 4). The yohimbine still appeared to protect the behavior against clonidine since no further reduction in LQ occurred with subsequent clonidine injection. The initial P induced heats in the Sprague-Dawley animals before any drug treatment seemed somewhat inferior to those of the Holtzman animals. No hopping and darting was seen, for instance.

TABLE 1

EFFECTS OF CLONIDINE, PIMOZIDE AND THEIR COMBINATION ON LORDOSIS QUOTIENTS OF ESTROGEN PRIMED, OVARIECTOMIZED RATS

Group	Drug (mg/kg)	n	LQ ±SE 0 hr	0.5 hr	1.5 hr	3.0 hr
1	Clonidine (0.125)	8	1 ± 1	2 ± 2	2 ± 2	—
2	Clonidine (0.400)	8	0	0	0	—
3	Pimozide (0.70)	6	12 ± 3	—	—	89.5 ± 5
4	Pimozide (0.70) + Clonidine (0.033)	14	2 ± 2	—	—	0

Drugs were injected at 0 hr, immediately after the test, except for the clonidine injection in Group 4, which was made at 1.5 hr.

*$p<0.001$.

TABLE 2

EFFECTS OF YOHIMBINE AND PIMOZIDE ON CLONIDINE SUPPRESSION OF LORDOSIS IN RATS TREATED WITH EB AND P

Group	Drug (mg/kg)	n	LQ ± SE 5 hr	LQ ± SE 6 hr	p
1	—	8	98 ± 3	45 ± 10	<0.001
2	Yohimbine (1)	11	98 ± 2	56 ± 13	NS
3	Yohimbine (2)	8	100	89 ± 5	<0.05
4	Yohimbine (5)	8	100	12 ± 12	<0.01
5	Pimozide (1)	7	100	14 ± 13	<0.01

Progesterone was injected at 0 hr, yohimbine and pimozide at 5 hr immediately after the test and clonidine at 5.5 hr. The statistical comparisons for Group 1 are between the 5 and 6 hr LQs. For Groups 2–5 the comparisons are between the 6 hr LQ and the 6 hr LQ of Group 1.

Another α-adrenergic antagonist, phenoxybenzamine, did not prevent the inhibitory action of clonidine on lordosis (Table 3). In one experiment phenoxybenzamine even appeared to potentiate the inhibition (Table 3, Group 3), but this effect was not repeated with a second batch of animals (Table 3, Group 4). By itself, phenoxybenzamine did not significantly alter the LQ (Table 3), though it did cause a noticeable degree of sedation, which was increased after clonidine treatment.

Since yohimbine, but not phenoxybenzamine, has been reported to increase lordotic responding in the absence of P [13], another agent which facilitates lordosis, pimozide [13], was tested to determine if it might also elevate responding in P treated animals given clonidine. On the contrary, pretreatment with pimozide significantly reduced the LQ below the level with clonidine alone (Table 2). The animals receiving this combination of drugs also displayed a substantial catatonia which was not seen after either drug alone.

Effects of Drug Injection on Lordosis Duration in EB, P Treated Rats

When the animals receiving clonidine and yohimbine were tested it was noticed that the lordosis posture frequently appeared to be held longer than in animals receiving only P. This was true even when the overall lordosis quotient was relatively low, as with the Sprague-Dawley animals. An even more stiking enhancement of the lordosis duration was noted in the group of animals given pimozide along with clonidine and P (Table 2). Six of the seven animals showed no lordosis whatever, but one had a lordosis quotient of 100 and held the lordosis posture for remarkedly long times, up to 10 sec.

TABLE 3

EFFECTS OF YOHIMBINE AND PHENOXYBENZAMINE ON LORDOSIS AND ON THE CLONIDINE SUPPRESSION OF LORDOSIS IN RATS TREATED WITH EB AND P

Group	Drug (mg/kg)	n	LQ ± SE Before Drug	LQ ± SE After Drug	LQ ± SE After Clonidine	p
1	—	7	98 ± 3	—	50 ± 13	<0.001
2	Yohimbine (2)	8	100	89 ± 5	89 ± 5	<0.05
3	Phenoxybenzamine (20)	7	97 ± 3	87 ± 7	23 ± 7	<0.007
4	Phenoxybenzamine (20)	5	94 ± 4	96 ± 4	49 ± 6	NS
5	Control (no clonidine)	8	100	100	100	<0.001

All groups (except 5) were given clonidine (33 μg/kg) ½ hr before the last test. Animals of Group 2 were tested 5 hr after progesterone, injected immediately with yohimbine, tested again 1 hr later, and immediately injected with clonidine. Animals of Groups 3 and 4 (two separate batches of ovariectomized animals) were tested 4 hr after progesterone, injected immediately with phenoxybenzamine, tested again 2 hr later and injected immediately with clonidine. All Group 5 animals were given 1 ml/kg saline in place of clonidine. Five of them also received 1 ml/kg 50% propylene glycol. Since the data from these two subgroups were the same they are combined in the table. For Group 1 the p value is for a comparison between the before drug and after clonidine LQ results. For Groups 2–5, the after clonidine LQ is compared with the after clonidine LQ of Group 1.

TABLE 4

EFFECTS OF YOHIMBINE ON LORDOSIS AND ON CLONIDINE INHIBITION OF LORDOSIS IN SPRAGUE-DAWLEY RATS TREATED WITH EB AND P

Group	Drug (mg/kg)	n	LQ ± SE Before Drug	LQ ± SE After Drug	LQ ± SE After Clonidine
1	Saline	8	96 ± 2	96 ± 3	48 ± 7
2	Yohimbine (2)	9	100	58 ± 6 *	56 ± 8
3	Yohimbine (2)	10	88 ± 5	47 ± 10 *	64 ± 9

Groups 2 and 3 were treated as Group 2 in Table 3.
*$p<0.001$.

TABLE 5

EFFECTS OF YOHIMBINE AND PHENOXYBENZAMINE ALONE AND IN COMBINATION WITH CLONIDINE ON THE DURATION OF LORDOSIS IN RATS TREATED WITH EB AND P

Group	(Table)	Drug (mg/kg)	n	Duration ± SE (sec) Before Drug	After Drug	After Clonidine
2	(3)	Yohimbine (2)	8	1.22 ± .05	0.94 ± .09 *	1.19 ± .13 *
2	(4)	Yohimbine (2)	9	0.82 ± .09	0.80 ± .05	0.92 ± .08
4	(3)	Phenoxybenzamine (20)	5	0.98 ± .05	1.25 ± .08 *	0.98 ± .14
3	(4)	Control (no clonidine)	8	0.85 ± .08	0.85 ± .06	1.11 ± .10

The data are from the same animals as in Tables 3 and 4.
*$p<0.025$.

In order to quantitate the apparent enhancement of lordosis duration by clonidine, the durations of individual lordosis responses for each animal were recorded on a cumulative stopwatch and the final sum was divided by the number of responses to obtain an average duration. When an individual response exceeded 1.5 sec its duration was also noted down.

As seen in Table 5, there were only slight changes in the average lordosis duration after clonidine or other drugs. Nevertheless, a number of individual responses were distinctly larger after injection of clonidine and yohimbine than before. In control groups few responses were over 1.5 sec (3/94) and none exceeded 2.0 sec, while after drug treatment a number (9/65) exceeded this value and ranged up to 3.5 sec. The range of individual durations in animals receiving phenoxybenzamine was the same as in controls though the drug did appear to increase the average duration slightly.

Effects of Drug Injections on Other Measures of Receptivity

The acceptance ratio and the lordosis intensity were also determined in the present experiments, but only a few significant changes were noted after drug treatments. The acceptance ratio was elevated in animals receiving pimozide or 5 mg/ml yohimbine along with clonidine, but these rats were also strongly debilitated. After clonidine alone the intensity of lordosis in P treated animals dropped from 2.0 to 1.2 ($p < 0.01$, n = 21).

DISCUSSION

The α-adrenergic agonist clonidine not only failed to facilitate lordotic responding in EB primed animals, but also substantially reduced the response level in animals brought into a receptive state with P or pimozide. This reduction did not appear to be due to sedative effects of the drug, since these are not reported at the dose utilized (33 μg/kg) [14] and were not apparent in the present animals. Furthermore, other agents with sedative effects, reserpine and phenoxybenzamine [14,27] do not interfere with lordosis [29]. Clonidine at 33 μg/kg would be expected to lead to hypotension [21,41] and possibly hypothermia [42], but again, reserpine [17] and phenoxybenzamine [42] also produce these physiological changes without affecting lordosis. It should be noted, however, that clonidine does suppress a number of different kinds of behavior (vi), and its effect on lordosis may well not be specific.

Pretreatment of animals with the α-adrenergic antagonist, yohimbine, prevented the effect of clonidine on the lordosis quotient. Even in experiments with Sprague-Dawley animals in which yohimbine itself had a suppressive effect on lordosis, it still blocked any further inhibition by clonidine. Yohimbine is reported also to facilitate lordosis without P [13,27] but another agent with a facilitative effect, pimozide [13], did not elevate responding in clonidine treated animals. In fact, the lordosis quotient was reduced to a level below that of clonidine alone, perhaps as a result of the cataleptic effect of the drug combination.

The present findings that an α-adrenergic agonist suppresses lordotic responding in rats treated with P and that this suppression can be reversed with the α-antagonist yohimbine provide evidence for an α-adrenergic system with an inhibitory control over lordosis. The demonstration that yohimbine itself facilitates lordosis in the absence of P [13] also supports the existence of such a system, though the possibility that yohimbine may act through adrenal P [29] must be considered. Phentolamine, another α-antagonist, has, in fact, been shown to activate adrenocortical secretion [32]. An old report that yohimbine greatly facilitates lordosis in male mice, however, would tend to argue against an involvement of adrenal P [11], since males are not sensitive to this steroid.

There are two immediate difficulties with this notion of an α-adrenergic, inhihitory system. First another α-antagonist, phenoxybenzamine, unlike yohimbine, neither reversed the effect of clonidine nor facilitated lordosis in the absence of P [13]. Second, results obtained in the guinea pig by Crowley *et al.* [6] do not agree with the present findings in rats. Not only did clonidine facilitate rather than inhibit lordosis in the former species, but phenoxybenzamine, which was without effect in rat, abolished responding. Both of these discrepancies, however, can be resolved by considering the possibility that there are two kinds of α-adrenergic receptor.

The evidence for two, or possibly more, kinds of α-adrenergic receptor in the brain has become substantial in the last few years, much of it arising from experiments with clonidine and various α-antagonists. Though it may oversimplify the situation somewhat, the physiological actions of these drugs can in general be divided into two groups, α_1 and α_2. α_1 actions are of a depressant nature and include sedation [7, 9, 27], EEG synchronization [14], hypo-

thermia [42], hypotension and other cardiovascular changes [23, 33, 34] and suppression of food [24] and water [25] intake and of conditioned reflexes [8]. In many cases these effects have been shown to be blocked by certain α-antagonists, such as, yohimbine and piperoxane, but not by some other antagonists, especially phenoxybenzamine [7, 8, 9, 14, 23, 24, 25, 33, 34]. This latter drug, on the other hand, unlike the α_1 drugs, is effective against another set of actions of clonidine, α_2, which are excitatory and include facilitation of the hindlimb flexor reflex [1, 2, 5], potentiation of the increase in locomotor activity induced by apomorphine [2, 3, 27] and stimulation of agressive behavior [28]. The catecholamines themselves appear to have both α_1 and α_2 like effects when injected into the lateral ventricle [20, 30, 44] or the hypothalamus [40]. For instance, in low doses NE causes an excitation [30,44] that can be blocked by phenoxybenzamine [20], but not by yohimbine [30,44], while in higher doses it produces a sedation that is insensitive to phenoxybenzamine [20] but can be reversed with yohimbine [30,44].

The suppression of lordosis by clonidine in the present experiments, then, can be understood as due to α_1 receptors, since it was blocked by yohimbine but not by phenoxybenzamine. The latter drug also lacked any suppressive effect itself on lordosis, and α_2 receptors would not seem to be critically involved in lordosis in the rat. These results do not support the possibility that NE has an important faciliatory role in the control of lordosis in this animal, at least through α-receptors, and the lack of deleterious effects from NE depletion by reserpine [29] also go against this notion. The β-receptors in rat also appear to be more inhibitory than facilitatory [43]. Most of the evidence in favor of facilitation by NE is in fact rather weak [13]. For instance, amphetamine was reported to enhance LQ slightly in rats given a dopamine receptor blocker [13], but this result could be explained simply as due to the antagonism by amphetamine of the cataleptic effect of the blocker [45], rather than to any stimulation of NE receptors specifically involved in lordosis.

Nevertheless there was some evidence in the present experiments that clonidine, in the presence of an α_1 block by yohimbine, could increase lordosis duration somewhat in the rat as well as in the guinea pig. The weakness of this effect was perhaps partially due to the low dose of clonidine, since α_2 actions generally require higher doses [2,5], or perhaps to some antagonism by the yohimbine. It is clear from the present results that this drug can suppress lordosis, possibly through stimulation of serotonin receptors [12,31] or through muscle weakness [45].

In the guinea pig, the evidence for a facilitatory effect of NE is quite strong. Clonidine, instead of suppressing lordosis, increases the duration of the responses [6]. That this latter action is due to α_2 receptors is suggested by the fact that the α_2 antagonist phenoxybenzamine itself greatly reduces the duration, eventually blocking responding entirely [6]. Further, in the guinea pig, unlike the rat, reserpine blocks lordosis, even in a low dosage where sedative effects are not prominent (Paris, unpublished results). Reserpine, of course, also depletes dopamine and serotonin as well as NE, but in both guinea pig [6] and rat [13] the former two bioamines seem to have inhibitory influences on lordosis. The apparent absence of an α_1 like effects of clonidine on lordosis in the guinea pig could be due to an insensitivity to the drug, and Crowley (personal communication) has noted that this species also shows very little sedation in response to clonidine, unlike a variety of other species. The drug, however, does produce profound hypotension in the guinea pig at doses similar to those effective in rats [12], suggesting that the guinea pig does possess α_1 receptors sensitive to clonidine.

It is interesting to speculate that the relative prominence of the α_2 system in guinea pigs could be related to some important differences between the sexual behavior of this animal and that of the rat. For instance, guinea pigs hold the lordotic posture much longer than do rats, for around 10 sec. compared to about 1 sec. It is conceivable that an α_2 system, which could work through direct facilitation of spinal reflexes [1, 5, 8, 15], is necessary for this greater duration. Further, the guinea pig, unlike the rat, possesses a mechanism for rapidly terminating heat after coitus. While the rat shows a relatively small loss of receptivity after repeated coital experience [19], the guinea pig goes out of heat after a single intromission [16], much as it does after an injection of phenoxybenzamine [6].

In summary, then, there appears to be two α-adrenergic systems which can influence lordosis in rodents. Whether or not either of these has any role in the normal physiological control of lordosis is still very much an open question. These systems show a highly differential distribution among the two rodent species studied. The α_2 system appears to be involved with lordosis in both rat and guinea pig, but it is far more important in the latter animal. Conversely, the α_1 system is weak or absent in the guinea pig, but prominent in the rat.

The underlying physiological nature of these two adrenergic systems is presently unknown. The α_2 receptors are most likely simply the postsynaptic receptors of nonadrenergic synapses, but the location of the α_1 receptors is more problematic. They may also be postsynaptic, but at some special class of adrenergic synapse, perhaps where epinephrine rather than NE is the transmitter [5]. There is indirect evidence that some α_1 actions of clonidine could be mediated through cholinergic [8, 9, 33] or histaminergic [21] synapses. However, the fact that the α_1 antagonist yohimbine facilitates lordosis [11,13], while the anticholinergic atropine is ineffective [26] does not support cholinergic involvement in the suppression of lordosis by clonidine.

Other possible bases for the α_1 actions of clonidine are the α-antagonist properties noted in cyclic AMP studies [35], or the inhibitory effects on NE release mediated through presynaptic receptors [36, 37, 38, 2, 10]. The ineffectiveness of phenoxybenzamine on lordosis would not support the first possibility, and arguments have been marshalled against the second possibility as well [18,22]. In view of the weak α_1 action of clonidine in the guinea pig it is interesting that the drug enhances, rather than suppresses, the release of NE in this animal [39]. Further studies with this species in comparison with the rat could be of value for a greater understanding of the nature and significance of the α-adrenergic systems in the brain.

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