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Role of Monoamines in Sexual Behavior of the Female Guinea Pig[1]

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CROWLEY, W. R., H. H. FEDER AND L. P. MORIN. *Role of monoamines in sexual behavior of the female guinea pig.* PHARMAC. BIOCHEM. BEHAV. 4(1) 67–71, 1976. – Ovariectomized guinea pigs, rendered sexually receptive by injections of estradiol benzoate and progesterone, were treated with drugs that are known to affect monoamine receptor activity. Treatment with the dopamine receptor stimulant apomorphine or the serotonin agonist LSD resulted in a suppression of lordosis behavior that lasted for several hours. The noradrenergic receptor stimulant clonidine potentiated the performance of lordosis (i.e., increased the duration of individual lordosis responses), while the noradrenergic receptor blocker phenoxybenzamine abolished sexual receptivity. Administration of dopaminergic or serotonergic receptor blockers (pimozide and methysergide, respectively) did not facilitate lordosis. In fact, methysergide produced a brief inhibition of sexual behavior. The results indicate that noradrenergic neurons may be involved in the induction of female sexual behavior in the guinea pig. Dopamine, and possibly serotonin, may serve as transmitters that inhibit lordosis in this species.

Norepinephrine Phenoxybenzamine Sexual behavior Apomorphine Clonidine
Serotonin Methysergide LSD Dopamine Pimozide

IN ovariectomized guinea pigs, estrogen administration is usually an insufficient hormonal stimulus for restoration of typical female sexual behavior. However, when progesterone is administered 24–48 hr after estrogen, the expression of female sexual responses is facilitated both in terms of the number of animals displaying lordosis and in terms of the intensity of the lordosis responses. In addition to this facilitatory effect on sex behavior, progesterone also possesses inhibitory influences on lordosis in guinea pigs and other mammals. A recent study by Morin and Feder [25] illustrates some of these facilitatory and inhibitory properties of progesterone. When ovariectomized guinea pigs were given estradiol benzoate (EB) systemically and then given progesterone (P) systemically 44 hr later, approximately 80 percent of the females showed lordosis responses. On the average, the maximum duration of the lordosis responses was 15 sec. However, when an intracranial implant of progesterone was interposed (at 36 hr) between the two systemic injections, lordosis responses occurred in only 41 percent of animals, and the maximum lordosis duration was significantly shortened in these animals to 10 sec. The anatomical site of this inhibitory effect of intracranially implanted progesterone on lordosis was the substantia nigra of the midbrain.

The substantia nigra is known to contain a large concentration of dopaminergic (DA) cell bodies whose axons innervate the neostriatum [8]. In view of this fact, we hypothesized that the lordosis inhibitory effect of progesterone implanted in the substantia nigra was mediated by activation of the nigro-striatal DA system. In order to test this hypothesis, ovariectomized guinea pigs were given EB and P systemically to induce lordosis. Then, while lordosis behavior was being displayed, the guinea pigs were given drugs known to stimulate or block DA receptors. Because other monoamine systems also course near the substantia nigra in their ascent to the forebrain [28], the effects of drugs that influence serotonin (5-HT) and noradrenergic (NE) receptor activity were also assessed.

METHOD

Animals

Female Hartley strain guinea pigs, 60–70 days old, were obtained from a commercial supplier (Camm Research, Wayne, N.J.). Animals were housed 8–10 per cage in a room with lights on from 0500 to 1900 hr and given unlimited access to Purina guinea pig chow and water.

Procedure

Three weeks after ovariectomy, all animals received at 1600 hr a subcutaneous injection of 3.3 μg EB in 0.1 ml

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sesame oil, and 36 hr later, an injection of 0.6 mg P administered subcutaneously in 0.1 ml oil. Starting 2 hr after P administration, animals were tested at hourly intervals for lordosis behavior by using the manual stimulation technique of Young *et al.* [33]. The duration of lordosis maintained during manual palpation was measured in seconds, and females were considered sexually receptive if they displayed lordosis of at least 1 sec duration on two consecutive hourly tests.

Experiment 1: Monoamine receptor stimulation. When an animal was considered to be sexually receptive, it was randomly assigned to receive 1 of 4 drug treatments: clonidine HCl (100 μg/kg of salt, IP), a potent and specific NE receptor stimulant [4]; apomorphine HCl (3.5 mg/kg base IP), a specific stimulant of DA receptors [5]; LSD (100 μg/kg, IP), a drug thought to stimulate central 5-HT receptors [1,3]; or isotonic saline vehicle (1 ml/kg, IP). Manual tests for lordosis were given 0.5 hr, 1 hr, and 1.5 hr following drug treatment and thereafter at hourly intervals until 12 hr after P injection (up to 5.5 hr postdrug for most animals).

Experiment 2: Monoamine receptor blockade. The protocol followed in Experiment 2 was identical to that of Experiment 1. After they displayed lordosis on two consecutive tests, animals received, in place of the monoamine receptor stimulants, one of the following monoamine receptor blockers: phenoxybenzamine HCl (20 mg/kg base in 50 percent propylene glycol, SC), a potent and relatively long lasting alpha-adrenergic antagonist [6,9]; pimozide (0.5 mg/kg dissolved in 0.2 N acetic acid and diluted with saline, IP), a blocker of central DA receptors [2]; methysergide maleate (10 mg/kg of salt IP in saline), a putative 5-HT receptor blocker [15,19]. Controls received vehicle injections in the same volume and by the same route of injection. Postdrug behavioral tests were conducted as in Experiment 1.

In both experiments, hormone and drug injections, and most of the behavior testing were done during the light phase of the cycle.

RESULTS

Experiment 1

Table 1 presents mean lordosis durations on the test immediately prior to drug treatment and on subsequent postdrug tests up to 4.5 hr. The data from each behavioral test were subjected to one-way analyses of variance followed by Dunnett's *t*-tests for comparing all means with a control [32]. None of the four treatment groups differed in predrug lordosis durations. The DA receptor stimulant apomorphine significantly suppressed the display of lordosis in the 0.5 hr, 1 hr and 1.5 hr postdrug tests (p's between 0.05 and 0.01, 2-tailed). One hour after injection, only 3 of 9 apomorphine-treated animals showed lordosis to manual stimulation, while all 10 saline-treated animals remained receptive (Fisher's exact $p<0.01$, 2-tailed). On the 2.5 hr, and all subsequent tests, no differences in lordosis duration between apomorphine and saline groups were noted, as the lordosis durations of the apomorphine-treated animals increased to the levels shown by the saline controls. Likewise, a transient inhibition of lordosis was seen in animals treated with the 5-HT agonist LSD. Lordosis durations were significantly reduced (p's between 0.05 and 0.01, 2-tailed) on the 0.5 hr, 1 hr and 1.5 hr tests and at 1 hr postdrug, only 3 of 10 LSD-treated animals displayed lordosis (Fisher's exact $p<0.01$, 2-tailed, vs. saline). After these tests, lordosis durations increased in the animals given LSD and subsequently did not differ from the saline controls.

Table 1 also indicates that mean lordosis durations were significantly increased 0.5 hr, 1 hr and 1.5 hr after administration of the NE agonist clonidine (p's between 0.05 and 0.01). Eight of 11 animals given clonidine held the lordosis posture for 30 sec or longer during manual stimulation in the first 1.5 hr after receiving clonidine.

The drug dosages were chosen on the basis that they produce behavioral and neurochemical changes in rats [3, 4, 5]. None of the drug treatments resulted in general behavioral excitation or in sedation or debilitation in the animals

TABLE 1

EFFECTS OF MONOAMINE RECEPTOR STIMULATING DRUGS ON LORDOSIS BEHAVIOR OF OVARIECTOMIZED GUINEA PIGS GIVEN 3.3 μG ESTRADIOL BENZOATE AND 0.6 MG PROGESTERONE 36 HR LATER

		Mean (± SE) Lordosis Duration (sec)						
Group	n	Predrug	Postdrug 0.5 hr	1 hr	1.5 hr	2.5 hr	3.5 hr	4.5 hr
Saline	10	11 ± 2	13 ± 2	15 ± 3	12 ± 2	17 ± 3	14 ± 3	14 ± 3
Clonidine (100 μg/kg)	11	10 ± 3	24 ± 5*	27 ± 4*	20 ± 4*	12 ± 3	8 ± 2	13 ± 2
LSD (100 μg/kg)	10	8 ± 2	3 ± 1*	5 ± 2†	3 ± 2*	12 ± 4	15 ± 5	17 ± 5
Apomorphine (3.5 mg/kg)	9	8 ± 3	3 ± 1*	3 ± 1†	2 ± 1*	10 ± 5	15 ± 6	16 ± 6

Receptor stimulating drugs were given after females displayed lordosis for 2 hr in response to estrogen and progesterone
*$p<0.05$ vs saline †$p<0.01$ vs saline

TABLE 2

EFFECTS OF MONOAMINE RECEPTOR BLOCKING DRUGS ON LORDOSIS BEHAVIOR OF OVARIECTOMIZED GUINEA PIGS GIVEN 3.3 μG ESTRADIOL BENZOATE AND 0.6 MG PROGESTERONE 36 HR LATER

		Mean (± SE) Lordosis Duration						
Group	n	Predrug	Postdrug 0.5 hr	1 hr	1.5 hr	2.5 hr	3.5 hr	4.5 hr
Vehicle	14	12 ± 2	20 ± 3	16 ± 3	12 ± 2	18 ± 3	14 ± 3	16 ± 3
Phenoxybenzamine (20 mg/kg)	7	12 ± 3	4 ± 1*	2 ± 1*	0.4 ± 0.4†	0	0	0
Pimozide (0.5 mg/kg)	5	12 ± 3	12 ± 5	12 ± 3	18 ± 3	17 ± 2	12 ± 2	11 ± 2
Methysergide (10 mg/kg)	6	15 ± 2	15 ± 3	10 ± 3	11 ± 4	5 ± 2	4 ± 2*	12 ± 5

Receptor blocking drugs were given after females displayed lordosis for 2 hr in response to estrogen and progesterone
*$p<0.05$ vs vehicle †$p<0.01$ vs vehicle

used in this study. No stereotypic behaviors (e.g. sniffing, gnawing) were observed in guinea pigs that received LSD or apomorphine. Most animals initially resisted manual palpation by running away and continued to do so after drug administration.

Experiment 2

The data from the animals that received monoamine antagonists were subjected to the same statistical tests as in Experiment 1. No differences in duration of lordosis were noted among animals that received injections of the propylene glycol, acetic acid or saline vehicles throughout the 12 hr test period. Therefore, for purposes of analysis, the data from these control groups were combined. None of the three drug treatment groups differed from vehicle-injected controls in the predrug tests. However, as shown in Table 2, administration of the alpha-adrenergic blocker phenoxybenzamine resulted in a gradual decrease in sexual behavior, so that by 2.5 hr, none of the phenoxybenzamine-treated animals displayed lordosis to hand stimulation. Table 2 also shows that at the dose level used, the DA receptor blocker pimozide failed to induce a significant alteration in lordosis duration or in the percent of animals showing lordosis. Likewise, the 5-HT antagonist methysergide had no effect on lordosis during the first several hours after its administration. However, on the 2.5 and 3.5 hr postdrug tests, only 3 of 6 animals displayed lordosis, and mean lordosis durations were significantly reduced ($p<0.05$, 2-tailed) on the 3.5 hr test. Methysergide- and vehicle-treated animals did not differ on subsequent tests.

Neither catalepsy nor other signs of behavioral depression appeared in animals treated with the monoamine antagonists.

DISCUSSION

Role of DA

In the present study, dopaminergic receptor stimulation (by apomorphine) produced a transient suppression of lordosis behavior in sexually receptive guinea pigs. That is, apomorphine decreased the number of animals showing lordosis and reduced lordosis durations. In a previous experiment [25], similar effects were obtained when progesterone was implanted into the substantia nigra, an area in which DA perikarya are concentrated. Thus, the results of the present experiment are consistent with our hypothesis that progesterone may act to inhibit lordosis by increasing activity of nigro-striatal DA neurons. Our results are also in agreement with recent experiments with rats. Apomorphine and ET495, another DA agonist, have been reported to suppress sexual receptivity in estrogen/progesterone-primed female rats [11,23], while DA receptor blockers facilitate lordosis in ovariectomized-adrenalectomized, estrogen-primed females [11,12].

Role of 5-HT

A brief cessation of lordosis behavior was seen after administration of LSD. Aghajanian *et al.* [1] and Andén *et al.* [3] have presented evidence that LSD has 5-HT mimicking properties in brain. Everitt *et al.* [12] found that, in doses of 5–20 μg/kg, LSD enhanced lordosis in estrogen-primed female rats, an effect they attributed to prevention of 5-HT release. However, these investigators and Meyerson *et al.* [23] have also reported that higher doses (40–100 μg/kg) suppress lordosis in estrogen/progesterone-primed rats. Both groups have suggested that the results with the higher doses of LSD are due to activation of 5-HT receptors. This proposal is in keeping with the theory of serotonergic inhibition of lordosis that was first proposed by Meyerson [22], and has been supported by recent experiments [11, 12, 23, 31, 34]. The results of the present study, which employed a 100 μg/kg dose of LSD, also tend to support the idea of serotonergic inhibition of lordosis in guinea pigs, but the inhibition of lordosis by LSD could have been caused by a number of other central and peripheral actions of LSD. It should be noted that the guinea pig

mesencephalon avidly concentrates labelled progesterone [30]. It is possible that this steroid induces midbrain 5-HT neurons to inhibit lordosis, but this notion has not been tested.

Because the DA receptor stimulant apomorphine and the 5 HT receptor stimulant LSD both caused decrements in lordosis in estrogen/progesterone-treated guinea pigs, one might expect that DA and 5-HT receptor blockers would cause increments in lordosis of estrogen-progesterone-treated animals. This was not the case. Neither pimozide, the DA antagonist, nor methysergide, the 5-HT antagonist, caused increases in lordosis behavior. In fact, some inhibitory effects of methysergide were obtained. It is possible that we employed doses that were not optimal. However, the dosage levels used in the present experiment have been shown to be effective in blocking DA and 5-HT receptors in rats [2,19]. Alternatively, one aspect of the lordosis-facilitatory action of progesterone may be to reduce activity in DA and 5-HT pathways. Indeed, progesterone has this action in estradiol-primed rats under certain conditions [12,14]. If this were true of guinea pigs as well, then blockage of the postsynaptic receptor in a system whose state of activity was already low would not be expected to produce any greater functional effect. A third possibility is that DA and 5-HT stimulation mimics the lordosis-inhibiting effects of progesterone. In order to detect an effect of DA or 5-HT antagonists on lordosis, it may be necessary to administer such drugs after sexual receptivity has terminated. These various possibilities are currently under investigation.

The finding that methysergide produced some inhibition of lordosis 2–3 hr after its administration raises questions concerning the role of 5-HT in sexual behavior of the female guinea pig. Recently, Haigler and Aghajanian [16] have called into question the potency of peripheral 5-HT antagonists, including methysergide, in blocking the action of 5-HT at central synapses. However, this drug has been shown to facilitate lordosis in rats after systemic [17,34] or central [7,31] application. Perhaps the effects obtained in the present study are indicative of species differences in response to the drug. Alternatively, it is known that receptor blockers produce a compensatory increase in monoamine turnover [13]. It may be that the brief inhibition of lordosis seen 2–3 hr after methysergide is the result of a drug-induced increase in 5-HT turnover. Further experiments with drugs that possess more specific actions on central 5-HT neurons need to be performed in order to more clearly define the role of this neurotransmitter in mediating female sex behavior in the guinea pig.

Role of NE

Noradrenergic receptor stimulation enhanced the display of lordosis, while blockade of NE receptors suppressed sexual behavior. These somewhat unexpected findings suggest that estrogen and/or progesterone may increase activity in central NE systems. Support for this idea comes from work with rats. Everitt *et al.* [11,12] found that amphetamine, a drug that promotes catecholamine release, potentiated the effect of DA receptor blockers in inducing lordosis. This drug combination presumably results in a selective activation of NE receptors. Amphetamine also partially restored female sexual behavior impaired after anterior hypothalamic lesions [18]. Furthermore, Kalra *et al.* [20] have demonstrated that the increase in LH secretion induced by treatment of ovariectomized rats with estradiol and progesterone is mediated by noradrenergic mechanisms. These steroid hormones also reduce NE turnover in the brain stem and inhibit NE uptake into brain slices [12], and these findings may be indicative of increased NE receptor activity [27].

A controversy has developed over whether adrenal hormones necessarily contribute to the increases in lordosis seen when estradiol-primed rats are given monoamine depletors [10,26]. It is not likely that the lordosis-facilitatory effect of the NE agonist clonidine is due to release of adrenal hormones such as progesterone in guinea pigs. All animals had already received amounts of exogenous progesterone sufficient to induce lordosis. Furthermore, administration of additional exogenous progesterone, instead of clonidine, probably would not produce prolongation of individual lordosis responses [24]. Finally, NE blockade (by phenoxybenzamine), which has been reported to cause ACTH release in several species [29], produced an inhibition, rather than a facilitation of lordosis.

The results of this study are in accord with previous demonstrations of noradrenergic facilitation, and dopaminergic/serotonergic inhibition of sexual receptivity in rodents [11, 12, 23, 31, 34]. They also provide support for the contention that progesterone inhibits lordosis in guinea pigs by activation of DA, and possibly, 5-HT mechanisms. Three further lines of inquiry are suggested by these findings. First, experiments that differentiate between the lordosis-facilitatory and lordosis-inhibitory actions of progesterone in terms of central neurotransmitters need to be carried out. Second, monoamine neurotransmitters have been implicated in the control of anterior pituitary secretion [21]. The influence of monoamines on mating behavior may reflect their role in a neuroendocrine regulatory system that coordinates sexual behavior and gonadotropin release. The details of this coordination remain to be examined both in rats and in guinea pigs. Third, the possibility that the drugs used in the present study altered the responsiveness of the animals to sexual sensory stimuli has to be examined. For example, the immobilization required by the lordosis posture may be incompatible with the motor activation that is usually produced by dopaminergic stimulation.

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