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Comparison of the Action of Lysergic Acid Diethylamide and Apomorphine on the Copulatory Response in the Female Rat

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Abstract. The effects of lysergic acid diethylamide (LSD) and apomorphine were compared using female copulatory behavior (lordosis response), in ovariectomized estrogen + progesterone-treated rats. Both serotonin and dopamine are implicated in the inhibition of this behavior. Each compound inhibited lordosis behavior dose dependently and with a similar time-course. Pimozide (0.1; 0.5 mg/kg) blocked the apomorphine (0.2 mg/kg)-induced decrease of lordosis response, while only a certain abbreviation of the LSD (0.10 mg/kg) inhibition was achieved by pimozide (0.5 mg/kg). Chlorpromazine (0.5 mg/kg) in a dose without effects on lordosis of its own had an action similar to pimozide on the LSD effect.

It is concluded that the predominant action of LSD on the female copulatory response is not mediated by increased dopamine receptor activity but that the LSD effect might be modulated by decreased dopaminergic activity.

Key words: Copulatory behavior – Dopamine – Serotonin – Lysergic acid diethylamide – Apomorphine – Pimozide – Dopamine antagonism – Chlorpromazine.

The most widely studied component of sexual behavior in female rats is the lordosis response. This behavior pattern is displayed by receptive females in response to being mounted by the male and consists of an arching of the back concomitant with an elevation of the head and rump, and deviation of the tail. After castration lordosis is abolished, but it can easily be reinstated by estrogen followed after an appropriate time interval by progesterone (Beach, 1942; Boling and Blandau, 1939). There is a dose-dependent relationship between the hormone treatment and the lordosis response, measured as in the present investigation (Meyerson, 1964a, 1967).

Accumulating data indicate monoaminergic involvement in the control of the lordosis response. Meyerson (1964a, b), testing a large number of compounds with different effects on monoaminergic transmitter mechanisms, found the most pronounced inhibitory effects after treatments that increase serotonergic (5-HT) receptor activity, which pointed to the existence of serotonergic neurons mediating inhibition of the female copulatory behavior. Later research, while adding further evidence for this conclusion, has shown that, in addition, muscarinic compounds exert certain inhibitory actions on the lordosis response in ovariectomized and hormone-treated female rats, providing that 5-HT also is available (Lindström, 1971). Recently, also dopamine has been implicated in the control of lordotic behavior of estrogen + progesterone-treated (Meyerson et al., 1973) and in estrogen-treated ovariectomized female rats (Everitt et al., 1974, 1975). The exact relationship between the estrogen + progesterone-and estrogen only-activated lordosis response is not entirely clear, but increased 5 HT and dopamine receptor activity seem to be inhibitory in both cases.

Lysergic acid diethylamide (LSD) is considered to be a central nervous system 5-HT agonist in certain doses (Andén et al., 1968; Aghajanian et al., 1972), and has in a previous investigation been found to inhibit the estrogen + progesterone-activated lordosis response dose-dependently (Eliasson and Meyerson, 1976). The present study deals with the effects of the dopamine receptor-stimulating agent, apomorphine (Andén et al., 1967; Ernst, 1967), in comparison with LSD on the lordosis response for a further clarification of dopamine and 5-HT involvement in the inhibition of lordosis by LSD. Recent reports claiming that LSD also influences dopaminergic

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receptors (DaPrada et al., 1975; Pieri et al., 1974; von Hungen et al., 1974) make a direct comparison of LSD and a dopamine agonist, tested under identical conditions on the same function, of great importance for the understanding of the functional effects of these two compounds. The actions of LSD and apomorphine were explored also after blockade of dopamine receptors by pimozide (Janssen et al., 1968), and dopamine + noradrenaline receptors by chlorpromazine (CPZ) (Andén et al., 1970) in a further attempt to differentiate the influence by LSD on different monoaminergic pathways. Selective blockers of central nervous serotonergic receptors do not appear to be available.

METHODS

Subjects

Sprague Dawley female rats (purchased as Specific Pathogen Free, Anticimex, Stockholm), weighing 250–300 g and ovariectomized at their arrival in the laboratory, served as subjects. They were housed in stainless steel cages with tap water and commercial rat pellets (Anticimex, 210 and R 3) available ad lib. The room was maintained at a temperature of 21 ± 1° C and had a reversed light-dark cycle (light from 9:00 p.m. to 9:00 a.m.).

The stud Wistar males, selected for sexual vigor and with considerable sexual experience, were kept in the same room as the females, housed in (40 × 40 × 30 cm) individual cages.

Materials Injected

The hormones used, estradiol benzoate (EB) and progesterone (both from Organon), were dissolved in olive oil and injected subcutaneously. Apomorphine HCl, lysergic acid diethylamide tartrate (LSD, both from Sandoz), and chlorpromazine HCl (CPZ) Hibernal®, Leo, ampoules 25 mg/ml) were all dissolved in saline. Pimozide (Janssen Pharmaceuticals) was dissolved in glacial acetic acid, diluted with saline, and the pH was adjusted to 5 by adding 2N NaOH. Apomorphine, CPZ, and pimozide were injected subcutaneously, while LSD was given by the intraperitoneal route. Doses mentioned in the text and tables always refer to the forms of the compounds stated above.

Behavioral Observations

Lordosis. Before testing with drug, the females were tested with a standard dose of hormones for an assessment of lordosis frequency in comparison with the laboratory standard. EB, 10 µg/kg, was followed 48 h later by progesterone, 0.4 mg/animal. The hormones were given at 8:00 a.m. and testing commenced at noon and continued at certain intervals during the afternoon. The frequency of responding in each test group (see below) used did not come below 75%.

Testing for drug effects took place 2 weeks following standardization and was performed under identical conditions. A predrug test was done at noon to ascertain that the hormone treatment had taken effect. Both CPZ and pimozide were injected 1 h before LSD and apomorphine, which were tested beginning at 2:00 p.m.

The females were tested individually in the home cage of the males where a maximum of six mounts was allowed and only absence or presence of lordosis was scored. To be rated as positive the female had to show lordosis of a certain quality (with head and perineum raised and the tail deviated). The percentage females showing lordosis in a given treatment group was calculated in two ways:

1) Total response, i.e., two consecutive lordoses out of a total of six mounts. And in addition,

2) Early response, i.e., two consecutive lordoses already in the first three mounts.

Percentage females showing a positive response with fewer mounts is obviously not independent from total lordosis response; however, this more demanding criterion can provide additional data of use for the interpretation of pharmacologic actions on copulatory behavior.

Locomotor Activity. As a measure of their locomotor ability the animal subjects were tested for 10 min in an activity meter (Animex®, Farad Inc., Hägersten, Sweden). The animals had the same hormone treatment and were tested at times analogous to the test for copulatory behavior. The sensitivity of this instrument was adjusted to record only gross motor activity across the cage bottom surface under which six oscillator coils are mounted. Movements across this electromagnetic field causes a change in its tuning which is automatically recorded on a cumulative counter.

Statistical Treatment of Data

The animals were divided into groups of 6–12 members. Each treatment was investigated in at least two replications. The experimental animals were used only once. Differences between groups of independent subjects with different treatments were analyzed statistically by means of the χ^2-test (Siegel, 1956) for lordosis frequency. Locomotor activity was subjected to an analysis of variance test followed by Dunnett's test for comparison of the treatment groups with the control group (Winer, 1971). The relationship between total lordosis response and lordosis within three mounts was calculated by means of the Spearman rank correlation test (Siegel, 1956).

RESULTS

In a previous investigation LSD 0.25 mg/kg was found to inhibit completely the lordosis response 10 min after the injection (Eliasson and Meyerson, 1976). From the results in Table 1 it is apparent that also the low dose, 0.05 mg/kg, of LSD had a significant inhibitory effect on lordosis, as indicated by the χ^2-test ($\chi^2 = 6.17$, df 1; $P < 0.02$). Apomorphine, likewise, had a dose-dependent relationship to lordosis inhibition and it significantly decreased the percentage females showing lordosis at 0.2 mg/kg ($\chi^2 = 16.45$, df 1; $P < 0.001$). Both LSD and apomorphine showed their maximal inhibitory effects on lordosis at the first test, 10 min after the injection. Recovery from this effect had commenced at the following test 30 and 50 min later respectively. With the highest dose of apomorphine tested, 0.5 mg/kg, there were significantly fewer recovered lordosis responses, as compared to the group receiving 0.2 mg/kg of this drug, still at the 60 min test ($\chi^2 = 15.03$, df 1; $P < 0.001$). Lordosis inhibition induced by 0.5 mg/kg of apomorphine was accompanied by pronounced behavioral stereotypies, such as sniffing and licking with a marked decrease of interest for the environment. Only a very small degree or sniffing that easily was interrupted by environmental stimuli was observed in connection

Table 1. Effects of different doses of lysergic acid diethylamide (LSD) and apomorphine (Apo) on the lordosis response in ovariectomized and estradiol + progesterone-treated rats

Treatment	mg/kg	Percentage females showing lordosis[b]				
		Pre-injection	10	40/60[a]	90/120[a]	*n*
Saline		73 (60)	82 (65)	86 (79)	86 (79)	57
LSD	0.05	83 (67)	42 (25)	83 (42)	83 (83)	24
	0.10	87 (58)	35 (13)	48 (54)	91 (88)	40
Apo	0.05	92 (79)	92 (79)	96 (88)	96 (88)	24
	0.20	93 (83)	40 (14)	88 (47)	93 (83)	58
	0.50	84 (54)	18 (10)	56 (34)	92 (78)	50

[a] LSD was tested 10, 40, and 90 min and Apo was tested 10, 60, and 120 min postinjection. Controls have been pooled since there were no differences between groups tested according to either schedule.
[b] The percentage females showing lordosis was calculated in two ways, see Methods. The data given in brackets are 'early response'.

Table 2. Lordosis responding after pimozide pretreatment continued with lysergic acid diethylamide (LSD) or apomorphine (Apo) in ovariectomized and estradiol benzoate + progesterone-treated rats

Treatment	mg/kg	Percentage females showing lordosis[b]				
		Pre-injection	10	40/60[a]	90/120[a]	*n*
Pimozide	0.1	92 (67)	92 (75)	100 (83)	100 (100)	12
	0.5	94 (83)	94 (91)	97 (97)	97 (97)	34
Pimozide + LSD	0.1 + 0.1	100 (67)	0 (0)	75 (25)	100 (75)	12
Pimozide + LSD	0.5 + 0.1	83 (79)	63 (33)	83 (50)	100 (75)	24
Pimozide + Apomorphine	0.1 + 0.2	83 (58)	75 (58)	92 (75)	92 (83)	12
Pimozide + Apomorphine	0.5 + 0.2	92 (78)	94 (78)	97 (86)	97 (86)	36

[a] and [b] See Table 1.

with testing of the 0.2 mg/kg dose. Occasionally very short and shallow lordosis-resembling movements were seen in response to the males' mounting, but devoid of such features as head and perineum elevation. These responses, which did not fulfill our criteria for lordosis, were only observed 10 min after injection of the drug. The 0.10 mg/kg dose of LSD was accompanied by a certain loss of motor coordination at the 10 min test; the hind legs of the animals were splayed, something that was completely reversed at the following testing occasion. Other drug-induced changes were decreased reactions to the cage environment except for certain stimuli, both visual and auditory, which could evoke exaggerated startles and at times flight responses. These effects had ceased at the 40 min test.

Pimozide while not significantly altering lordosis percentage on its own in either dose prevented lordosis inhibition by apomorphine 0.2 mg/kg partially at the 0.1 mg/kg dose and completely at 0.5 mg/kg of pimozide (Table 2). This latter effect showed a high degree of statistical significance in the comparison with 0.2 mg/kg of apomorphine alone ($\chi^2 = 24.69$, $df\,1$; $P < 0.001$). Pimozide in either dose together with LSD, on the other hand, did not significantly alter the effect of this drug. The females seemed more alert than after LSD alone and showed a high degree of resistance to the male's mounting attempts. At the 40 min test, the percentage drug-treated females responding with lordosis was indistinguishable from a saline-injected control group (Tables 1 and 2), i.e., more females had recovered from the treatment of pimozide 0.5 mg/kg and LSD 0.10 mg/kg than from this dose of LSD alone, an effect which was statistically significant ($\chi^2 = 5.09$, $df\,1$, $P < 0.05$). However, this effect was not seen in the early response measure. Otherwise, the frequency of lordosis within the three first mounts, was influenced by the treatments in ways similar to the total response measure of lor-

Table 3. Lordosis responding after chlorpromazine (CPZ) pretreatment combined with lysergic acid diethylamide (LSD) or apomorphine (Apo) in ovariectomized and estradiol benzoate + progesterone-treated rats

Treatment	mg/kg	Percentage females showing lordosis[b]				
		Pre-injection	10	40/60[a]	90/120[a]	*n*
A. CPZ	0.5	85 (70)	85 (45)	85 (24)	85 (79)	33
CPZ	1.0	75 (67)	33 (8)	33 (0)	42 (42)	12
B. CPZ	0.5 +	88 (63)	29 (4)	79 (67)	96 (79)	24
LSD	0.1					
C. CPZ	0.5 +	92 (79)	54 (25)	79 (50)	96 (71)	24
Apo	0.2					

[a] and [b] See Table 1.

Table 4. Mean locomotor activity ($n = 10$) for different treatments

Treatment mg/kg	Score
Saline	833
LSD, 0.10	600
Apomorphine, 0.20	572
CPZ, 0.5	534
CPZ, 0.5 + LSD, 0.1	532
CPZ, 0.5 + Apo, 0.2	421
Pimozide, 0.5	303
Pimozide, 0.5 + LSD, 0.1	544
Pimozide, 0.5 + Apo, 0.2	568

P compared to saline (Dunnett's test) for all treatments < 0.01. Test at 10 min after last injection.

dosis as evident from Tables 1 and 2. This is further indicated by a high rank order coefficient. Amount of stimulation from the male for lordosis display within three mounts showed a very close agreement with total lordosis frequency ($r_s = 0.97$, $n = 16$, $P < 0.01$).

Chlorpromazine, 1.0 mg/kg, significantly prevented the lordosis response in comparison with the saline-treated group at the first testing occasion ($\chi^2 = 7.47$, $df\,1$; $P < 0.01$, Table 3). No influence of this compound on the lordosis response was observed by the 0.5 mg/kg dose, given 1 h before testing. When combined with LSD, a dose of 0.5 mg/kg CPZ had no effect in preventing the lordosis inhibition by the former agent, however in the 40 min test more subjects with this treatment combination had recovered than after the same dose of LSD alone ($\chi^2 = 4.99$, $df\,1$; $P < 0.05$). There were no significant effects obtained on the apomorphine-induced lordosis inhibition by CPZ.

Effects on Locomotor Exploratory Activity

Table 4 presents the results of the different treatments, when tested on locomotor behavior. This provides a background against which the lordosis data can be interpreted, the assumption being that a drug or a combination of drugs that severely impairs one form of motor behavior could similarly interfere with the motor expression of another function—in this case, lordosis. All treatments employed here interfere to some extent with locomotor exploratory behavior, which is also shown by a highly significant effect on the analysis of variance test ($F = 15.84$, $df\,8/81$; $P < 0.01$). Subsequent comparisons between the means of the saline control and all other conditions, utilizing Dunnett's test showed that every treatment gave a significantly impaired performance on the locomotor test, as compared to the control group at this particular level of significance. A Spearman rank correlation test between lordosis inhibition and effects on locomotor behavior for the presently considered treatments does not indicate any relationship between impairment on the two tests ($r_s = -0.19$, $n = 9$, N.S.).

DISCUSSION

The present data and previous experiments with a higher dosage range (Eliasson and Meyerson, 1976) demonstrate that LSD has a dose-related inhibitory effect on lordosis responding in the estrogen + progesterone-treated ovariectomized female rat. Apomorphine similarly induces a dose-dependent decrease of the percentage of females showing lordosis in response to being mounted by a male. Both compounds have a relatively short duration of action on the lordosis response with recovery from a significant suppression of the response appearing within an hour of injection. Biochemical studies of the clearance rate of LSD from the brain (Rosecrans et al., 1967) have demonstrated that LSD in doses comparable to those in the present study and larger had essentially disappeared from the brain 30 min after injection. Concomitant with this was the duration of gross behavioral changes these authors observed after

LSD treatment, a time course that agrees well with the effects of LSD on lordosis. The lordosis inhibition seems to be a specific effect, since it also appears in the absence of any clear stereotypies in the case of apomorphine, and without any gross motor incapacities, as in the case of the lowest dose of LSD. Both of these behavior disturbances could be expected to interfere with the display of the copulatory behavior.

Pimozide, an agent that has been demonstrated to be relatively specific in its capacity to block dopamine receptors without any serotonin blocking action (Janssen et al., 1968; Jacobs, 1974), did not in the presently considered doses have any significant effects on the percentage of lordosis-responding females. However, practically all females showed lordosis already before the pimozide treatment why a stimulatory effect is not seen, but cannot be excluded. Enhancement of lordotic responding by pimozide in higher doses has been found in female rats treated with estrogen only (Everitt et al., 1974, 1975). When combined with LSD or apomorphine there was a differential effectiveness in the ability of pimozide to block the lordosis inhibition by these two compounds in equipotent doses. There was no prevention of the LSD inhibition of lordosis responding by the lower dose of pimozide. On the contrary, even resistance to the male's mounting attempts was noted. The main effect of 0.5 mg/kg pimozide, when given before LSD, was to shorten the duration of the action of this drug. On the other hand, when the dopamine receptor blocking agent was combined with apomorphine there was an effective prevention of lordosis inhibition by this drug at the same dose of pimozide, implying a direct effect on dopaminergic neurons. The differential effects by LSD and apomorphine emerge even more clearly, when results, using the more demanding criterion of two consecutive lordoses in three mounts, are considered.

CPZ is cited in the clinical literature as a compound with the capacity to block behavioral effects of LSD when administered before the latter drug (Abramson, 1956; Hoch, 1955; Isbell and Logan, 1957), even though attempts to replicate these effects under somewhat more controlled conditions have failed to demonstrate any significant modifications of the LSD effects by CPZ (Clark and Bliss, 1957). Studies of animal behavior using dose ranges comparable to the present ones seem to indicate an effect of CPZ in shortening the duration of an LSD-induced disruption of performance rather than decreasing the LSD effect (Ray and Marazzi, 1961; Appel and Freedman, 1964). There are many procedural differences between studies, however the main influence of CPZ on lordosis inhibition by LSD agrees with the findings of the previous studies.

The lack of correlation between locomotor disturbance and lordosis inhibition supports the impression that the decrease of the copulatory response frequency obtained in the present study is not due to impaired motor functions, but is rather an effect on pathways in the brain mediating lordosis inhibition.

The parallel effects by LSD and apomorphine in decreasing lordosis responding could be mediated by serotonergic and dopaminergic receptor influence respectively, although some dopaminergic effects by LSD cannot be entirely excluded. However, the relative lack of an effect of pimozide in preventing the LSD inhibition of the lordosis response indicates that the predominant effect of LSD on the lordosis response is not a direct influence on dopaminergic receptor activity. Since CPZ and pimozide, had an effect only on the duration rather than on the magnitude of LSD inhibition of lordosis, their influence could be related to the metabolism or distribution of LSD rather than a direct action. However, an alternative hypothesis could be based upon the assumption of an interdependent network of pathways controlling the lordosis response. Instead of LSD acting directly on dopaminergic receptor sites the LSD action could be modulated by dopaminergic activity. This interpretation would be in line with the present and previous data taken together showing that decreased dopaminergic activity achieved by dopamine antagonism as well as impaired catecholamine biosynthesis by α-MT (Eliasson and Meyerson, 1976) led to a slight decrement particularly shorter duration of the LSD action on the female copulatory response.

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