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ENHANCEMENT BY PROGESTERONE OF LYSERGIC ACID DIETHYLAMIDE INHIBITION OF THE COPULATORY RESPONSE IN THE FEMALE RAT

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Copulatory behavior in the ovariectomized rat, the lordosis response (L.R.) was induced by either estrogen alone or estrogen followed by progesterone. L.R. has been shown to be inhibited dose-dependently by lysergic acid diethylamide (LSD). The effects of various hormone treatments on the LSD-induced inhibition were tested in the present study. Progesterone but not estrogen was found to significantly enhance the LSD effect in a dose-dependent manner. In contrast, the effect of LSD on spontaneous behaviors in an exploratory situation was not influenced by progesterone treatment. This phenomenon of increased L.R. inhibitory effect by LSD was probably not due to a steroid-induced change in LSD metabolism. The data show instead that progesterone specifically influences monoaminergic mechanisms, which are related to the action of LSD. This has important implications for the possibility that progesterone induces the L.R. by acting on monoaminergic mechanisms.

Female lordosis response Copulatory behavior Progesterone LSD
Exploratory behaviors

1. Introduction

Among the hormone-activated elements of female sexual behavior the one most thoroughly studied is the copulatory response (lordosis posture) shown by a receptive female rat when mounted by a male. The lordosis response disappears after ovariectomy but can be restored dose-dependently by estrogen followed after a certain time by progesterone treatment (Boling and Blandau, 1939; Meyerson, 1964a; Meyerson and Eliasson, 1977). Estrogen alone is less effective in producing the behavior but restores the response to a certain level after repeated daily injections (Davidson et al., 1968).

A possible relationship between monoaminergic mechanisms and the hormone-dependent behavioral response has been suggested (for reviews see Meyerson and Eliasson, 1977; Meyerson and Malmnäs, 1978). A large body of evidence has accumulated, suggesting that there is a serotonergic system which mediates inhibition of the copulatory response in the female rat. Dopamine has also been shown to be implicated in the control of the female sexual behavior, i.e. increased dopaminergic activity inhibited the female lordosis response. These conclusions have been reached in studies in which brain monoamine activity was selectively influenced with various pharmacological tools, such as monoamine-oxidase inhibitors, monoamine precursors, receptor stimulating and blocking agents, amine depletors and synthesis inhibitors (Eliasson and Meyerson, 1973; Everitt et al., 1974, 1975; Meyerson, 1964a, b, c;

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Meyerson et al., 1974; Meyerson and Lewander, 1970).

Although psychopharmacological data support the idea that monoaminergic pathways are involved in the control of female copulatory response, the hormone-monoamine relationship remains to be clarified. The purpose of the present experiments was to investigate the possibility that endocrine and monoaminergic mechanisms interact directly in the control of sexual behavior. As stated above, earlier data demonstrated that hormone-induced sexual responses are inhibited or facilitated by certain psychotropic compounds. It was shown i.a. that lysergic acid diethylamide (LSD) dose-dependently inhibited the estrogen + progesterone-activated lordosis response in the female rat (Eliasson and Meyerson, 1976, 1977). In the present experiments we examined the influence of various treatment regimens of estrogen and progesterone on the lordosis inhibiting effect of LSD.

2. Materials and methods

2.1. Animals and laboratory conditions

The subjects were female Sprague-Dawley rats (Specific Pathogen Free, Anticimex, Sollentuna, Sweden, weighing 300—350 g). They were ovariectomized (under ether anesthesia) on arrival in the laboratory and randomly divided into groups of 5—6 animals which were kept in stainless steel cages with tap water and commercial rat food pellets available ad libitum. Light was provided from 9 pm to 9 am and the temperature kept at 21—22°C. Sexually active Wistar male rats were housed in the same room as the females, placed in (40 × 40 × 30 cm) individual cages which also served as testing cages.

2.2. Behavior elements and testing procedures

Lordosis response (L.R.): the female was transferred to a sexually vigorous male and the absence or presence of L.R. on mounting by the male was recorded. Each female received 6 mounts. A positive score meant a clear-cut L.R. (head and perineum raised, tail deviated) on at least two consecutive mounts. The percentage of subjects which showed L.R. was calculated for each treatment. For an assessment of lordosis frequency, the females were tested two weeks before the experiment without drugs but with a standard dose of hormones (estradiol benzoate, 10 μg/kg followed 48 h later by progesterone 0.4 mg/animal). The frequency of responding in each test group ranged between 75—100%. The hormones were injected at 8 am and testing commenced 4—5 h after the progesterone treatment. On the day of drug testing a pre-drug test was run one hour before the drug injection to test the effectiveness of the hormone treatment. LSD injections were always given 5 h after progesterone treatment. At this time the lordosis behavior had developed fully and the response remained on a plateau for a few hours during which the drug effect could be tested.

Spontaneous behaviors: The animal was transferred to an empty observation cage (48 × 35 × 36 cm, plexiglass front, floor covered with shavings) and certain behavoir elements were recorded during 10 min of direct observation. The observer used a switchboard connected to an electronic device which recorded the latency (sec) of onset, frequency and duration (sec) of the behaviors studied. The following elements were recorded. Sniffing: rapid movements of whiskers, with snout close to different objects while generally exploring the environment. Investigating: intense sniffing directed at a particular object like a shaving, a fecal blob etc., sometimes picked up by the animal and explored. Rearing: standing on the hindlegs. Resting: laying or standing without any particular overt behavior. In addition, ambulation was measured automatically (Animex, Farad Inc., Hägersten, Sweden). The sensitivity of the activity device was set to measure locomotor activity. The activity is given as counts/10 min recording.

Statistical treatment of data: each treatment was investigated in at least two replications using independent groups. The differences between groups of subjects with different treatments were analysed statistically by means of the χ^2 test, Fisher's exact probability test, or Mann-Whitney U-test (Siegel, 1965). Treatments to be compared were run simultaneously in parallel test sessions.

Materials injected: 17β-estradiol benzoate (EB) and progesterone both from (Sigma), isopregnenone (6-dehydroretroprogesterone, Ferrosan, Malmö, Sweden) were dissolved in olive oil. Hormones were injected in a volume of 0.25—0.35 ml. Lysergic acid diethylamide tartrate (Sandoz) was dissolved in saline and injected intraperitoneally (i.p.) in a volume of 1 ml/kg. The doses refer to the salt.

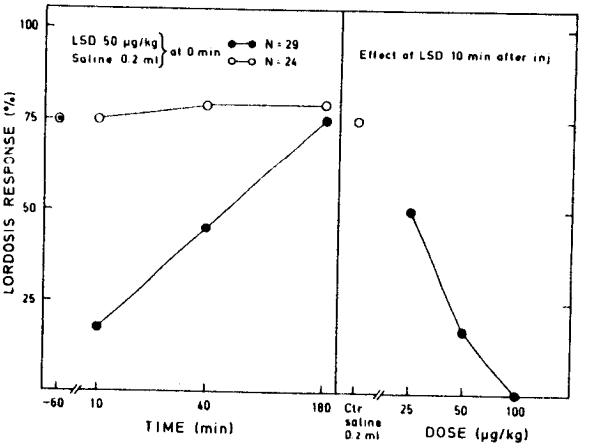

Fig. 1. Effects of lysergic acid diethylamide (LSD) on estradiol benzoate (EB) + progesterone-activated lordosis response in ovariectomized rats, time-response (left) and dose-response (right) relationships. EB, 10 µg/kg, was given 48 h before progesterone 0.4 mg/rat. LSD or saline was injected at 0 min, 5 h after progesterone treatment.

3. Results

3.1. The inhibitory effects of LSD; dose- and time-reponse relationships

The study started with experiments carried out to establish the dose of LSD necessary for a submaximal or maximal effect and the optimal time interval after injection under the present experimental conditions. The effect of LSD 50 µg/kg on the EB (10 µg/kg) + progesterone (0.4 mg/animal)-activated L.R. is depicted in fig. 1. The maximal inhibition was obtained 10 min after the LSD injection ($\chi^2 = 13.6$, $P < 0.01$, vs. saline controls), at which time the inhibitory effect was clearly related to the dose. Full recovery of the female copulatory response was obtained 3 h after the LSD injection at all three dose levels.

3.2. Estrogen treatment and the effect of LSD

The relationship between the estrogen treatments (10 and 25 µg/kg), and the effect of LSD was studied with the dose of progesterone kept constant (table 1, A, B, D, E).

LSD, 50 µg/kg, produced a significant reduction of the L.R. after EB, 10 µg/kg as well as after EB, 25 µg/kg. When the percentage inhibition at 10 min after LSD injection was compared to the pre-drug response, there was a tendency for the LSD effect to be more pronounced when the higher dose of EB was used but this difference did not reach statistical significance.

3.3. Progesterone treatment and the effect of LSD

The influence of progesterone on the inhibitory effect of LSD was studied in two ways. First, lordosis responding was induced by estrogen alone and the estrogen was given in repeated doses. The LSD effect under these conditions was compared to that of LSD when progesterone was given as well (table 2). Second, lordosis was induced by estrogen and progesterone and the influence of different doses of progesterone on the LSD inhibition of lordosis was studied. Here two doses of estrogen and LSD, one high (table 3) and one low were used (table 1, EB 10 µg/kg).

When lordosis responding was induced by EB alone, in repeated doses (3 × 10 µg/kg),

TABLE 1

Effects of lysergic acid diethylamide (LSD) on the percentage of females showing a lordosis response activated by estradiol benzoate (EB) and progesterone

EB was given 48 h before progesterone. LSD or saline was injected at 0 min, 5 h after progesterone treatment.

	Treatment				Percentage lordosis				n [1]	
	EB μg/kg	Progesterone mg/rat	LSD μg/kg	Saline ml/rat	Min after last injection −60	10	40	180	Rats	Repl.
(A)	10	0.1	50		59	38 [2]	69	86	29	6
	25	0.1	50		67	29 [3]	71	90	24	4
(B)	10	0.4	50		84	13 [4]	54	85	41	7
	25	0.4	50		94	17 [4]	56	100	18	3
(C)	10	4.0	50		80	0 [4]	43	93	30	5
(D)	10	0.1		0.2	61	70	78	78	23	5
	25	0.1		0.2	63	83	83	79	24	4
(E)	10	0.4		0.2	72	79	83	79	29	5
	25	0.4		0.2	94	94	94	94	18	3
(F)	10	4.0		0.2	83	83	83	83	18	3

[1] n rats = number of rats; n repl. = number of replications.
[2] $P < 0.05$, [3] $P < 0.01$, [4] $P < 0.001$ (χ^2 test) for LSD compared to saline.

the lordosis frequency at the pre-drug test was 63% (table 2A). LSD, 100 μg/kg, slightly reduced the copulatory response. This effect did not reach statistical significance ($\chi^2 = 1.25$, N.S. 10 min test). The effect of LSD when 4 mg progesterone was given after

TABLE 2

Effects of lysergic acid diethylamide (LSD) on the percentage of females showing a lordosis response activated by estradiol benzoate (EB) alone or followed by progesterone.

EB was injected 29, 53 and 77 h before the LSD or saline treatment. Progesterone was given 24 h after last EB injection, 5 h before LSD treatment.

	Treatment	μg/kg	Percentage lordosis				n [1]	
			Min after last injection −60	10	40	180	Rats	Repl.
(A)	EB + LSD	10 (× 3) 100	63	44	72	91	32	5
	EB + saline	10 (× 3) 0.2 ml	63	63	67	67	24	4
(B)	EB + progesterone + LSD	2 (× 3) 4 mg 100	100	0 [2]	42	100	12	2
	EB + progesterone + saline	2 (× 3) 4 mg 0.2 ml	75	83	83	92	12	2

[1] n rats = number of rats; n repl. = number of replications.
[2] $P < 0.001$ (χ^2 test) for LSD compared to saline.

repeated injections of EB (3 × 2 μg/kg) is shown in table 2B. The dose of EB in this experiment was decreased so as to obtain a comparable pre-drug response level (75—100%). In spite of the fact that the pre-drug response was slightly higher than when EB was given alone, the effect of LSD was more pronounced. The difference in LSD effects between the progesterone and no-progesterone experiments was significant (table 2A and B, 10 min after LSD injection $\chi^2 = 5.82$, $P < 0.02$).

In the high-dose experiment (table 3) 100 μg/kg LSD completely inhibited the lordosis behavior 10 min after the injection. Recovery was somewhat faster when the lower dose of progesterone was given.

The relationship between progesterone and the inhibitory effect of LSD was studied further in one experiment in which the EB and LSD doses were adjusted to give a sub-maximal response level (table 1). A significant increase of the inhibitory effect of 50 μg/kg LSD was obtained by raising the dose of progesterone from 0.1 to 4 mg/rat (table 1A, B, C, EB 10 μg/kg, $\chi^2 = 10.24$ at 10 min, $P < 0.01$).

In a further experiment, another progestin, isopregnenone, which lacks the anesthetic properties of progesterone, was used as control for the enhancement by progesterone of the LSD-induced inhibition of the L.R. The data in table 4 show that even after a 'high' EB dose, LSD 100 μg/kg almost completely inhibited the estrogen + isopregnenone-induced response. At 40 min the response was more depressed with the higher dose of isopregnenone. However, this difference did not reach statistical significance ($\chi^2 = 1.2$ N.S.).

3.4. Spontaneous behaviors

The following experiment was done to study the influence of progesterone on the effect of LSD on some elements of behaviors other than sexual responses. The hormonal treatment was the same as the one used to activate L.R. The data are summarized in fig. 2. The two hormone treatments led to no differences in any of the behavior patterns measured (EB 2 μg/kg × 3 compared to EB 2 μg/kg × 3 + progesterone 4 mg/rat, Mann-Whitney U test: $45 < U < 84$ N.S.). Each behavior except resting, was seen at least once in all animals tested (n = 12). Resting was only seen in the LSD-treated subjects (100%).

LSD 100 μg/kg significantly (Mann-Whitney U test: $0 < U < 32$, $P < 0.05$) altered all behavioral measurements except investigating (duration, latency) and ambulation. The effect of LSD was, however, the

TABLE 3

Effects of lysergic acid diethylamide (LSD) on the percentage of females showing a lordosis response activated by estradiol benzoate (EB) and progesterone.

EB was given 48 h before progesterone. LSD or saline was injected at 0 min, 5 h after progesterone treatment.

Treatment EB, 25 μg/kg and			Percentage lordosis				n [1]	
Progesterone mg/rat	LSD μg/kg	Saline ml/rat	Min after last injection −60	10	40	180	Rats	Repl.
0.4	100		96	0 [2]	50 [2]	100	24	4
4.0	100		100	0 [2]	25 [2]	100	24	4
0.4		0.2	96	96	96	96	24	4
4.0		0.2	100	100	100	100	24	4

[1] n rats = number of rats; n repl. = number of replications.
[2] $P < 0.001$ (χ^2 test) for LSD compared to saline.

TABLE 4

Effects of lysergic acid diethylamide (LSD) on the percentage of females showing a lordosis response activated by estradiol benzoate (EB) and isopregnenone.

EB was given 48 h before isopregnenone. LSD was injected at 0 min, 5 h after isopregnenone treatment.

Treatment EB, 25 μg/kg and		Percentage lordosis				n [1]	
Isopregnenone mg/rat	LSD μg/kg	Min after last injection −60	10	40	180	Rats	Repl.
0.4	100	92	9	42	100	24	4
4.0	100	83	0	16	100	12	2

[1] n rats = number of rats; n repl. = number of replications.

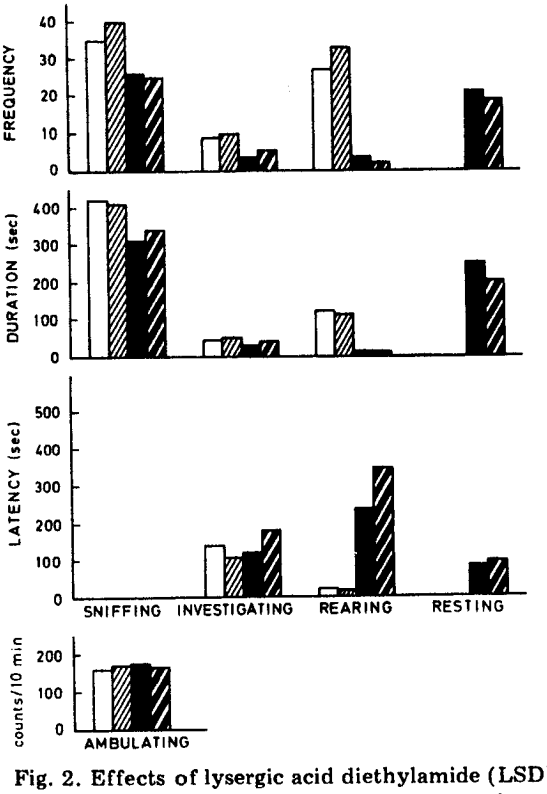

Fig. 2. Effects of lysergic acid diethylamide (LSD) on spontaneous behavior in an exploratory situation. The test was conducted 10 min after the LSD treatment. Number of animals tested in each treatment = 12. Number of replications = 2. The test lasted 10 min. The sniffing latency was ≤3 sec for all categories. Treatments: EB 2 μg × 3 □; EB 2 μg × 3 + progesterone 4.0 mg/rat ▨; EB 2 μg × 3 + LSD 100 μg/kg ■; EB 2 μg × 3 + progesterone 4.0 mg/rat + LSD 100 μg/kg ▨.

same in the progesterone-and non-progesterone-treated subjects.

4. Discussion

The inhibitory effect of LSD on the estrogen + progesterone activated L.R. reported earlier (Eliasson and Meyerson, 1977) was confirmed in the present study. LSD had a dose-related inhibitory effect on the L.R. in estrogen + progesterone-treated ovariectomized female rats. The maximal effect was obtained 10 min after injection. In the study of Everitt et al. (1975) small doses of LSD (5—20 μg/kg) facilitated the L.R. induced by estrogen alone. A higher dose (40 μg/kg) had no stimulatory effect and due to the low hormone-induced response level a significant inhibitory effect could not be shown.

In the present study even a high dose of LSD (100 μg/kg) did not have any significant influence on the response induced by estrogen alone. The response level in these experiment was such that it should have permitted a clear, significant inhibition to be observed. In contrast, the LSD treatment effectively inhibited the EB + progesterone-induced response. This could be seen when the response was induced in 100% of the animals and a high dose of LSD was used (100 μg/kg), and also at a lower dose of LSD (50 μg/kg), when the hormone treatment was adjusted to give a response level of 65—80%. A very clear-

cut inhibition was induced by LSD in the progesterone-treated rats regardless of whether EB was given at intervals or in one injection. The data presented also show that the effect of LSD was enhanced by increasing doses of progesterone.

It has been reported that progesterone had anesthetic properties (Meyerson, 1967). This effect was not obtained with isopregnenone which, however, is also effective to induce a L.R. The present study shows that the relationship between the inhibitory effect of LSD and the progesterone action does not seem to be connected with the anesthetic properties of progesterone, as the effect was also seen after isopregnenone treatment.

The possibility that various estrogen treatments also alter the effect of LSD on the L.R. is indicated by the present data, however, compared to the effect produced by progesterone the specific influence of estrogen does not seem to be significant. The effect might be explained by a synergistic relationship between the effect of progesterone and the estrogen treatment.

There is much evidence suggesting that serotonergic and dopaminergic neurons are involved in estrogen + progesterone-activated L.R. in the female rat. In certain doses LSD is considered to be a central nervous system 5HT-agonist (Andén et al., 1968; Aghajanian et al., 1972). A comparison of the action of LSD and the dopamine agonist apomorphine on the copulatory response has been carried out by Eliasson and Meyerson (1976) and it was concluded that the predominant action of LSD on the female copulatory response was not mediated by increased dopamine receptor activity, but rather that LSD influenced serotonergic activity. It is therefore reasonable to propose that the progesterone treatment found to influence the lordosis inhibitory effect of the postulated 5HT agonist LSD, influenced serotonergic mechanisms important for the efficiency of the LSD action. Thus, the present data suggest that progesterone influences the serotonergic mechanisms involved in the LSD action and the lordosis behavior. Our data are in agreement with the data of Espino et al. (1975) who found that the serotonergic agonist α-methyltryptamine blocked the facilitation of the L.R.by progesterone but had no effect on the L.R. induced by estrogen alone.

The possibility that progesterone interferes with LSD action in a non-specific way has, however, also to be considered. Alterations of LSD-induced effects by various steroid hormones including progesterone have been reported (Bergen et al., 1960; Krus et al., 1961). In these reports daily treatment with progesterone was shown to suppress the LSD effect on non steroid-dependent responses. To explain the present data on a non-specific basis one possibility would be that progesterone facilitated the metabolism of LSD and that more active lordosis inhibitory metabolites were obtained. In the rat, LSD is almost completely metabolized and at least four metabolites have been reported (Stoll et al., 1955; Boyd, 1959; Slayter and Wright, 1962; Siddik et al., 1975). Despite a considerable body of literature on the pharmacological effects of LSD there is still very little information as to the activity of its metabolites. Thus, the possibility that the effect of progesterone on LSD action on the L.R. was due to active metabolites cannot be fully excluded. However, progesterone did not influence the effect of LSD on the exploratory and locomotor elements which are not progesterone dependent responses. This would suggest instead, that the effect of progesterone on LSD action in the lordosis experiments was due to a direct action on serotonergic mechanisms implicated in the lordosis behavior. The exact nature of this interaction is unknown and has to be studied further.

Acknowledgements

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