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Lysergic Acid Diethylamide: Evidence for Stimulation of Pituitary Dopamine Receptors

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Abstract. Lysergic acid diethylamide (LSD), 0.05 mg/kg and 0.20 mg/kg, significantly decreased plasma prolactin (PRL) levels in male rats. LSD, 0.20 mg/kg, also inhibits the increase in plasma PRL levels produced by chlorpromazine (CPZ), 5 mg/kg, and alpha-methylparatyrosine (AMPT), 50 mg/kg, both of which interfere with dopaminergic inhibition of PRL secretion. LSD was more potent than methysergide, a serotonin receptor blocker, in lowering plasma PRL levels and more potent than apomorphine, a known direct acting dopamine agonist, in blocking the increase in plasma PRL produced by quipazine, a 5-HT agonist. These results suggest LSD has potent dopamine agonist properties on the rat pituitary or hypothalamic dopamine receptors which directly or indirectly inhibit PRL secretion.

Key words: Prolactin – LSD – Dopamine – Serotonin – Methysergide – Chlorpromazine – Quipazine – Alpha-methylparatyrosine – Apomorphine

The central effects of d-lysergic acid diethylamide (LSD) were initially attributed to antagonism of 5-hydroxytryptamine (5-HT) at central 5-HT receptors (Gaddam, 1953; Wooley and Shaw, 1954). Subsequently, the possible importance of LSD as a 5-HT agonist at pre- or postsynaptic 5-HT receptors (Andén et al., 1968; Aghajanian, 1972; Jalfre et al., 1974; Aghajanian and Haigler, 1975) or as an inhibitor of 5-HT release was emphasized (Chase et al., 1969). Recently, evidence for an agonist action of LSD at dopaminergic receptors has been presented. LSD produced circling toward the intact side of rats with unilateral 6-hydroxydopamine or 5,6-dihydroxytryptamine-induced lesions of the median forebrain bundle (Pieri et al., 1974; Boissier et al., 1976). Similar results are produced by the dopamine agonist apomorphine (Ungerstedt and Arbuthnott, 1970). In contrast with the above studies suggesting a significant dopamine agonist action for LSD, Milson and Pycock (1976) found that LSD (0.025–0.2 mg/kg) produced no consistent effect on apomorphine- or amphetamine-induced turning and had slight effect by itself on turning behavior in mice with unilateral 6-hydroxydopamine-induced lesions of the nigro-striatum. Grabowska and Michaluk (1974) observed only a slight effect of LSD on apomorphine-induced locomotor activity in rats, which led them to suggest it lacks potent dopamine agonist actions.

However, there is substantial additional evidence for agonist and antagonist effects of LSD at dopamine receptors. LSD *inhibited* dopamine-stimulated adenylate cyclase, which has been suggested to be part of the dopamine receptor (Iversen, 1975) from corpus striatum, cerebral cortices, and hippocampi of young adult rats (Von Hungen et al., 1974, 1975). However, LSD was also able to *stimulate* the adenylate cyclase of corpus striatum and this was antagonized by neuroleptic drugs as well as 5-HT blockers. Mescaline, N,N-dimethyltryptamine, psilocin, and bufotenin did not stimulate striatal adenylate cyclase. It was concluded that LSD is capable of acting as an agonist and antagonist at central dopamine and 5-HT receptors (Von Hungen et al., 1974, 1975; Da Prada et al., 1975). It has been suggested that d-LSD is a potent mixed dopamine agonist and antagonist as evidenced by its ability to compete with tritiated dopamine and haloperidol for binding to calf striatal membranes (Creese et al., 1975). LSD depressed the inhibitory responses to dopamine of Apylsia ganglionic neurons (Sato and Sawada, 1975). LSD in the rat decreased striatal and retinal homovanillic acid, the major metabolite of dopamine, and inhibited the decrease in dopamine levels following alpha-methylparatyro-

sine (Da Prada et al., 1975). It was also reported that in the cat LSD decreased the output of DA into the perfusate of the caudate nucleus (Da Prada et al., 1975). These results are consistent with the hypothesis that LSD decreases dopamine turnover in the brain as a result of dopamine receptor stimulation. LSD increased rat brain dopamine and decreased brain tyrosine, findings which are consistent with increased dopamine synthesis (Smith et al., 1975). LSD can produce stereotyped behavior in rats (Dixon, 1968; Fog, 1969). LSD and apomorphine stimulated locomotor activity in rats previously injected with 6-hydroxydopamine in the nucleus accumbens (Kelly and Iversen, 1975). The effect of LSD was not mimicked by bromo-LSD, a 5-HT antagonist, but was blocked by the dopamine antagonist pimozide. These results indicated that LSD acts as an agonist at mesolimbic dopamine receptors.

We were interested in studying the dopamine agonist properties of LSD via a neuroendocrine strategy. Dopamine agonists such as apomorphine and bromcryptine depress serum prolactin (PRL) levels in rats and man (Smalstig et al., 1974; Lal et al., 1973). This is probably due to direct action at dopamine receptors in the pituitary that inhibit PRL secretion (MacLeod, 1976; Brown et al., 1976; Massara et al., 1976). Conversely, dopamine antagonists increase serum PRL levels by preventing dopaminergic inhibition of PRL secretion (Lu et al., 1970). The fact that such neuroleptic stimulation of PRL secretion can occur in stalk-sectioned monkeys (Diefenbach et al., 1976) and that intravenous dopamine in man antagonizes the effect of neuroleptics (Meltzer et al., 1977c) is strong evidence for the effect occurring at the pituitary or the median eminence of the hypothalamus rather than in dopaminergic receptors protected by the blood-brain barrier.

LSD prevented the increase in serum PRL levels in female rats, which occurs on the afternoon of proestrous, and even lowered serum PRL levels below baseline (Quadri and Meites, 1971). These authors attributed this to an ergot alkaloid-like effect. However, they did not explicitly relate it to a dopaminergic agonist effect. It has been demonstrated that methysergide, which is like LSD in being an ergot alkaloid and a blocker of 5-HT receptors, can inhibit the estrogen-induced increase in PRL secretion (Caligaris and Talesnik, 1974). Subramanian and Gala (1976) found that methysergide can partially block the afternoon surge in plasma PRL in ovariectomized, polyestradiol phosphate-injected rats. Gallo et al. (1975) reported that methysergide inhibited the marked increase in plasma PRL produced by suckling, an effect believed to be due to its 5-HT receptor blocking properties. Thus, the inhibition by LSD of the proestrous-induced PRL release reported by Quadri and Meites (1971) might also be due to blockade of 5-HT receptors by LSD. Further, we have demonstrated that the indolealkylamine hallucinogens such as N,N-dimethyltryptamine, bufotenin, psilocybin, and related drugs such as mescaline and dimethoxyphenethylamine can increase plasma PRL levels in male rats, probably due to their ability to stimulate 5-HT receptors in the hypothalamus or pituitary (Meltzer et al., 1977b). We therefore decided to investigate further the effects of LSD on PRL secretion in the rat with a view to further studying its dopamine and 5-HT agonist or antagonist effects.

MATERIALS AND METHODS

Male Sprague-Dawley rats weighing 150 – 200 g were used throughout these studies. They were housed six to a cage in a temperature-controlled room with a 12-h light-dark cycle. They had free access to Purina rat chow and water.

All drugs were dissolved in saline and injected intraperitoneally (i.p.). Rats were injected with ketamine, 100 mg/kg i.p., prior to sacrifice. Ketamine does not affect plasma PRL in the rat (Lawson and Gala, 1974). Heparinized blood was obtained from the inferior vena cava within 3 min of injecting ketamine. Plasma samples were frozen and later assayed for PRL by a double antibody radioimmunoassay as previously described (Meltzer et al., 1975). PRL is expressed as ng/ml NIH rat PRL-RP-1. Data was analyzed by means of a one-way analysis of variance. The contrasts between groups was determined by the method of Scheffe or Duncan's Multiple Range Test (Kirk, 1968).

LSD was provided by the NIMH-FDA Committee on Scheduled Substances. Apomorphine was a gift of Merck, Sharp and Dohme, Rahway, New Jersey. Chlorpromazine (CPZ) was a gift of Smith, Kline and French, Inc., Philadelphia, Pennsylvania. Alpha-methylparatyrosine methylester (AMPT) and para-chlorphenylalanine methylester (PCPA) were purchased from Sigma Chemical Co. Methysergide maleate was a gift of Sandoz, Inc., East Hanover, New Jersey. Quipazine was a gift of Miles Laboratories, Elkhart, Indiana.

RESULTS

LSD in doses of 0.05 and 0.2 mg/kg significantly decreased rat plasma PRL levels in naive male rats (Table 1). There was no difference between the effect of either dose. Methysergide, 10 mg/kg, also significantly decreased rat plasma PRL levels (Table 1). Methysergide, 5 mg/kg, had no effect on plasma PRL levels (data not presented).

LSD in doses of 0.2 mg/kg and 0.5 mg/kg but not 0.05 mg/kg significantly inhibited the increase in PRL produced by CPZ, 5 mg/kg i.p. (Table 2). Apomorphine, at 0.5 mg/kg, significantly inhibited the effect of CPZ but the slight inhibitory effect of 0.20 mg/kg did not achieve statistical significance. There was no effect of apomorphine 0.05 mg/kg on the increase in plasma PRL produced by CPZ. The effect of LSD 0.2 mg/kg on the PRL response to CPZ was signif-

Table 1
Effect of LSD or methysergide on rat plasma PRL levels

Group	Treatment	Dose (mg/kg)	Plasma PRL (ng/ml)
1	Saline	—	5.5 ± 1.3
2	LSD	0.05	2.2 ± 0.6
3	LSD	0.20	2.1 ± 0.9
4	Methysergide	10	1.8 ± 1.3

ANOVA Table

T	ss	*df*	MS	F	
Treatments	47.00	3	15.67	13.70	$P < 0.01$
Errors	18.25	16	1.14		
Total	65.25	19			

Rats were injected with drugs 30 min prior to anesthetization with ketamine. All groups consisted of 5 rats. PRL levels are mean ± SD.
Contrasts: Group 2 vs. 1, $P < 0.05$; 3 vs. 1, $P < 0.05$, 4 vs. 1, $P < 0.05$; 3 vs. 2, NS. Contrasts were determined by the method of Scheffé (Kirk, 1968)

Table 2
Effect of LSD, apomorphine, and methysergide on increase in plasma PRL produced chlorpromazine

Group	Drug 1	Dose (mg/kg)	Drug 2	Dose (mg/kg)	Plasma PRL (ng/ml)
1	Saline	—	Saline	—	5.9 ± 1.6
2	Saline	—	CPZ	5	23.5 ± 12.9
3	LSD	0.05	CPZ	5	21.0 ± 13.2
4	LSD	0.20	CPZ	5	2.4 ± 0.9
5	LSD	0.50	CPZ	5	1.0 ± 0.2
6	APO	0.05	CPZ	5	21.2 ± 13.5
7	APO	0.20	CPZ	5	10.5 ± 3.0
8	APO	0.50	CPZ	5	4.4 ± 2.7
9	Methysergide	10	CPZ	5	23.6 ± 14.9

ANOVA Table

T	ss	*df*	MS	F	
Treatments	4046.33	8	505.79	5.94	$P < 0.05$
Error	3066.70	36	85.19		
Total	7113.03	44			

Rats were injected with first drug 15 min prior to second drug and anesthetized with ketamine 30 min later. All groups consisted of 5 rats. PRL levels are mean ± SD.
Contrasts: Group 2 vs. 1, $P < 0.05$; 3 vs. 2, NS; 4 vs. 2, $P < 0.05$; 5 vs. 2, $P < 0.05$; 6 vs. 2, NS; 7 vs. 2, NS; 8 vs. 2, $P < 0.05$; 9 vs. 2, NS; 7 vs. 4, $P < 0.05$. Contrasts were determined by the Duncan Multiple Range Test (Kirk, 1968)

icantly greater than that of the same dose of apomorphine. Methysergide at a dose of 10 mg/kg i.p. had no effect on the increase in plasma PRL produced by CPZ.

AMPT blocks dopamine synthesis by inhibiting tyrosine hydroxylase (Weissman and Koe, 1965). The decrease in dopaminergic activity leads to an increase in prolactin secretion (Voogt and Carr, 1975). Both LSD 0.2 mg/kg and apomorphine 5.0 mg kg significantly inhibited the increase in plasma PRL produced by AMPT, 50 mg/kg (Table 3). There was no significant difference between the effects of LSD and apomorphine.

Quipazine is a 5-HT agonist (Hong et al., 1969; Rodriquez et al., 1973) that like 5-hydroxytryptophan (5-HTP) increases rat serum prolactin levels (Meltzer et al., 1976). We have previously reported that the increase in PRL produced by quipazine is potentiated by pretreatment with PCPA and blocked by the dopamine agonists bromcryptine and apomorphine (Meltzer et al., 1976). LSD, 0.5 mg/kg, completely inhibited the increase in plasma PRL produced by quipazine, 5 mg/kg, in naive rats or rats pretreated with PCPA-methylester (Table 4). Methysergide, 5 mg/kg, also inhibited the increase in PRL produced by quipazine and PCPA plus quipazine, which agrees with previous results (Meltzer et al., 1976), but had no effect at doses less than 2.5 mg/kg i.p. (data not presented).

DISCUSSION

LSD lowered plasma PRL in male rats, in agreement with a similar finding in female rats (Quadri and Meites, 1971). The following considerations lead us

Table 3
Effect of LSD and apomorphine on the increase in plasma PRL produced by AMPT

Group	Drug 1	Dose (mg/kg)	Drug 2	Dose (mg/kg)	Plasma PRL (ng/ml)
1	Saline	–	Saline	–	6.8 ± 4.8
2	Saline	–	AMPT	50	38.6 ± 17.0
3	LSD	0.2	AMPT	50	1.2 ± 0.9
4	Apomorphine	5	AMPT	50	8.2 ± 7.0

Rats were given first injection 15 min prior to second injection and anesthetized with ketamine 30 min after second injection. All groups consisted of 5 rats. Plasma PRL levels are mean ± SD. Significant contrasts ($P < 0.05$) were as follows: 2 vs. 1; 3 vs. 2; 7 vs. 2. Groups 3 and 4 were not significantly different. Contrasts were determined by the method of Scheffé (Kirk, 1968)

ANOVA Table

T	ss	*df*	MS	F	
Treatments	4234.48	3	1411.49	15.38	$P < 0.01$
Error	1468.68	16	91.79		
Total	5703.16	19			

Table 4
Effect of LSD on increase in PRL produced by quipazine

Group	Treatment (dose)[a]	Prolactin (mg/ml)
1	Saline + saline + saline	5.8 ± 3.2
2	Saline + saline + quipazine (5 mg/kg)	13.4 ± 7.0
3	Saline + LSD (0.5 mg/kg) + quipazine (5 mg/kg)	2.0 ± 0.7
4	PCPA (300 mg/kg) + saline + quipazine (5 mg/kg)	48.5 ± 12.9
5	PCPA (300 mg/kg) + LSD (0.5 mg/kg) + quipazine (5 mg/kg)	1.1 ± 0.6

[a] All groups consisted of 5 rats
First injection (saline or PCPA-methylester, 300 mg/kg) was administered 24 h prior to second injection (saline or LSD). Third injection (saline or quipazine) was administered 15 min after second injection. Rats were anesthetized 15 min later with ketamine. PRL levels are mean ± SD. *Contrasts:* 2 vs. 1, NS; 3 vs. 2, $P < 0.05$; 4 vs. 1, $P < 0.05$; 5 vs. 4, $P < 0.05$. Contrasts were determined by the method of Scheffé (Kirk, 1968)

ANOVA Table

T	ss	*df*	MS	F	
Treatments	7862.95	4	1965.74	16.81	$P < 0.01$
Errors	2338.25	20	116.91		
Total	10201.20	24			

to conclude that this was the result of dopamine agonist properties rather than 5-HT antagonist properties. Methysergide has more potent central and peripheral antiserotonergic properties than LSD (Fanchamps et al., 1960). Although methysergide was able to lower plasma PRL levels, a far higher dose of methysergide than LSD was required, which suggests 5-HT receptor blockade is not the basis of the LSD-induced decrease in PRL levels. Behavioral and biochemical studies indicate that methysergide lacks dopamine agonist properties (Milson and Pycock, 1976; Boissier et al., 1976; Von Hungen et al., 1975) so its ability to lower PRL levels in the male rat is unlikely to be accounted for on that basis.

The ability of LSD but not methysergide to antagonize the increase in PRL produced by CPZ also suggests that LSD produces this effect by other than an antiserotonergic action. This effect of LSD is most likely due to a dopamine agonist action. Ergot alkaloids, to which LSD is chemically related, have been shown to be potent inhibitors of PRL secretion (Nagasawa and Meites, 1970). The potency of LSD as an antagonist of the CPZ-induced increase in plasma PRL was greater than that of apomorphine: e.g., LSD was significantly more potent than apomorphine at doses of 0.2 mg/kg.

Methysergide and another serotonin antagonist, SQ 10,631 [2-chloro-2[1]-[3-(dimethylamine) propyl] thio-cinnamanilide, HCl], partially inhibited the increase in plasma PRL produced in female rats by pimozide, a dopamine antagonist (Lawson and Gala, 1976). The authors attributed this partial blockade to the antiserotonin action of these drugs inhibiting a serotonin system that stimulates prolactin secretion rather than to a dopamine agonist action. The inhibitory effect of methysergide on the pimozide-induced PRL increase was slight and much less than the total blockade of the CPZ-increase in PRL produced in this study by much lower doses of LSD. The difference in sex of the rats in the two studies may account for

the difference in the effect of methysergide, since estrogens can affect the PRL increase due to phenothiazine (Buckman et al., 1976) and the estrogen effect may be blocked by methysergide (Subramanian and Gala, 1975).

The ability of LSD and apomorphine to antagonize the increase in plasma PRL produced by AMPT also suggests a direct DA agonist effect of LSD. Apomorphine and LSD under these conditions stimulate dopamine receptors directly and thus prevent the effects on PRL secretion of inhibition of DA synthesis by AMPT. The ability of LSD to antagonize the increase in PRL produced by quipazine, a serotonin agonist, even with the marked potentiation of the quipazine-induced increase by pretreatment with PCPA, is similar to the effect of apomorphine on the plasma PRL increase produced by 5-hydroxytryptophan (Meltzer and Fang, 1976) or quipazine (Meltzer et al., 1976). This antagonism is most likely due to the dopamine agonist rather than to the serotonin antagonist action of LSD since it was produced by relatively low doses of LSD compared to the more potent 5-HT antagonist methysergide.

The effect of LSD on PRL secretion in vivo in the male rat is consistent with the biochemical, behavioral, and physiological evidence (reviewed in the introduction) that LSD is a direct acting dopamine agonist. The pituitary dopamine receptors that regulate PRL secretion in the rat respond similarly to neuroleptic drugs compared to the dopamine receptors believed to mediate the antipsychotic action of the neuroleptics (Meltzer et al., 1977a, 1977c, 1977d). These latter dopamine receptors are believed to be in the meso-limbic region (Stevens, 1973; Meltzer and Stahl, 1976). Thus, the results reported here are further indication that LSD could be a potent agonist at meso-limbic dopamine receptors in man, as suggested by others (Kelly and Iversen, 1975). It is likely that this effect contributes to the hallucinogenic action of LSD but it is unlikely that it fully explains this action since such other dopamine agonists as apomorphine are not potent hallucinogens. The *combination* of agonist actions at 5-HT and dopamine receptors and antagonism at 5-HT receptors may be important factors in its hallucinogenic action.

The opposite effect of LSD and hallucinogens of the indolealkylamines and mescaline type on PRL secretion is additional evidence that LSD has a unique pharmacologic action compared to these agents. This is of interest in terms of the inability of rats to distinguish between the two drugs at comparable doses on the basis of interoceptive cues (Hirschhorn and Winter, 1971). It has previously been suggested that elevated cerebrospinal fluid (CSF) PRL levels may have behavioral effects (Clemens and Sawyer, 1974). Since CSF PRL levels are correlated with plasma PRL levels (Meltzer et al., unpublished data), this suggests that CSF PRL levels are not relevant to the ability to distinguish between internal states in the rat since mescaline increases plasma PRL levels (Meltzer et al., 1977b) while LSD lowers plasma PRL levels. Because they are all hallucinogens, one might argue that stimulation of dopamine receptors has nothing to do with the hallucinogenic action of these drugs since it has become commonplace to argue that only actions which these drugs have in common are relevant to their hallucinogenic action (Tonge and Leonard, 1969). It is likely that this is an unnecessarily restrictive requirement and that such unique properties as the dopamine agonist action of LSD may contribute in an important way to its hallucinogenic effects.

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