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Effects of Dopaminergic and Cholinergic Drugs, Naloxone and L-Prolyl-Leucyl-Glycinamide on LSD-Induced Catalepsy

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Summary. In an attempt to elucidate the mechanism of *d*-lysergic acid diethylamide (LSD) induced catalepsy, the effects of cholinergic and dopaminergic agents, naloxone and L-propyl-leucyl-glycinamide (PLG) were studied in rats. The dose-dependent (50–500 μg kg^{-1} s.c.) and time-related cataleptic response elecited by LSD was preceded by a phase of hyperexcitability. The non-hallucinogenic analogue, 2-bromo-LSD (BOL), was without effect. Both apomorphine, the dopamine agonist, and L-DOPA antagonized LSD-induced catalepsy whereas the dopamine depleting agent α-methyl-p-tyrosine (α-MPT) slightly prolonged the cataleptic effect. Cholinergic muscarinic receptor stimulation with pilocarpine antagonized LSD-induced catalepsy. The muscarinic antagonists, atropine and scopolamine, intensified the hyperexcitable phase and potentiated the cataleptic effects of LSD. Nicotine slightly potentiated LSD action but mecamylamine antagonized it. While pre-treatment with naloxone, the narcotic antagonist and PLG prolonged the cataleptic response, post-treatment with naloxone effectively attenuated LSD-induced catalepsy. The behavioural data are interpreted to suggest that LSD-induced catalepsy may be mediated through diminished dopaminergic and cholinergic neuronal activity and under enkephalinergic modulation. The neuroanatomical foci and exact mechanism of action remain to be delineated.

Key words: LSD – Catalepsy – Cholinergic drugs – Dopamine.

Introduction

The fundamental mechanism underlying the spectrum of behavioural effects elicited by *d*-lysergic acid diethylamide (LSD), a well-known hallucinogen, remains to be succinctly defined. Earlier neuropharmacological studies implicated 5-hydroxytryptamine as the primary neurochemical substrate subserving LSD-induced central effects (Aghajanian et al., 1970; Aghajanian, 1976). The functional activity of central 5-hydroxytryptaminergic neurons, however, does not necessarily reflect the degree of hallucinosis, since lisuride, an analogue of LSD devoid of any psychotomimetic effects in humans, produced a greater increase in 5-hydroxytryptamine turnover (Pieri et al., 1978). Furthermore, the high-affinity stereospecific binding site for LSD as described in neuronal membranes has not been demonstrated to correlate with either the psychotomimetic potency or possible antagonism of 5-hydroxytryptamine (Lovewell and Freedman, 1976).

On the other hand, evidence derived from biochemical, electrophysiological and behavioural studies suggests that LSD possesses dual dopamine agonist-antagonist properties. LSD, in alignment with the classical dopamine agonist apomorphine, caused contralateral rotational behaviour in 6-hydroxydopamine-lesioned rats (Pieri et al., 1974; Trulson et al., 1977) and effectively attenuated the firing rate of dopaminergic neurons in the substantia nigra (Christoph et al., 1977). Radioreceptor binding studies revealed potent interaction with central dopamine receptor as differentially labelled by ^{3}H-haloperidol (Creese et al., 1975) while the observed inhibitory effect of LSD on dopamine-sensitive adenylate cyclase activity (Bockaert et al., 1976) and the enhanced dopamine turnover (Persson, 1977a, 1977b) may be explained in terms of its dopamine antagonist activity.

Blockade of striatal dopamine receptors by neuroleptics has been shown to elicit in rodents catalepsy characterized by the maintenance of abnormal body postures, a major behavioural consequence of extrapyramidal motor dysfunction (Costall and Naylor, 1974). In view of recent interesting but controversial developments of LSD action, it would be worthwhile to

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examine the extent to which the alleged mixed dopamine agonist-antagonist activity displayed by LSD contributes towards the cataleptic state as recently observed by Fertnizer and Fischer (1978). Although the latter investigators considered the reversal of LSD-induced cataleptic response by naloxone, the narcotic antagonist, to be opiate specific, it appears equally likely that other putative neurotransmitters such as acetylcholine and dopamine may also play modulatory roles. In the present investigation, we attempted to study the influence of agents selectively affecting dopaminergic, cholinergic and peptidergic neurotransmission on LSD-induced catalepsy in the rat.

Materials and Methods

Subjects. Male Sprague-Dawley rats purchased from the Canadian Breeding Farm, Quebec, were used throughout the studies. The animals weighing between 200–250 g upon arrival were housed individually in plastic cages in temperature-controlled rooms maintained on a 12–12 h light-darkness cycle. They were allowed free access to food (Purina rat chow) and water, and to become acclimatized for at least 2 days prior to the start of the experiments. All rats were used only once for the study.

Drugs. LSD and 2-bromo-LSD (BOL) were kindly supplied by the Health Protection Branch, Health & Welfare Canada, Ottawa, Canada. Apomorphine was a gift from Merck Frosst Laboratory, Dorval, Canada, and carbidopa was a gift from Merck Sharp & Dohme, Kirkland, Quebec, Canada. Naloxone was a gift from Endo Laboratories, Garden City, New York, USA. Pilocarpine, methylatropine, methylscopolamine, α-methyl-p-tyrosine methyl ester (α-MPT) prolyl-leucyl-glycinamide (PLG), scopolamine, nicotine, hexamethonium and mecamylamine were obtained from the Sigma Chem. Co., St. Louis, Missouri, USA. Carboxymethylcellulose was bought from British Drug House, Chemical, Toronto, Ontario, Canada. Atropine sulfate was purchased from Sterilab., Downview, Ontario, Canada.

αMPT was suspended with 2% carboxymethylcellulose in saline solution. L-DOPA was suspended in 0.9% saline by rapid mixing immediately prior to injection. Atropine sulfate was available in solution dosage form commercially and used as such. Apomorphine was dissolved in 1% ascorbic acid; other drugs were dissolved in 0.9% physiological saline in volumes of 1 ml kg^{-1} of body weight, unless otherwise indicated. All doses were calculated as acid or base equivalent. All drugs were prepared immediately prior to use.

Procedure for Catalepsy Testing. At each experimental session the animals were transferred to a sound-attenuated room and allowed to habituate for at least half-an-hour. Throughout our studies we used the modified simple bar test as described previously by Ezrin-Waters and Seeman (1977) which entailed gently placing both front paws of the rats in extended positions on a horizontal metal bar mounted 10 cm above a wooden platform and measuring the time spent in maintaining this abnormal body posture. The animals were tested three times at each specified time interval after drug administration and the maximal cataleptic response attained in the three trials was reported in seconds, the cut-off time limit being set at 120 s. All drug treatments and behavioural testing were carried out between 9 am and 7 pm.

Drug Dosing Schedules. To examine the temporal profile of the dose-dependent relationships, four randomly assigned rats were challenged with LSD at the doses of 50, 250, 375 and 500 μg kg^{-1} subcutaneously and the intensity of the cataleptic reaction was evaluated at 30, 60, 90, 120, and 180 min.

For the drug interaction studies, 375 μg kg^{-1} s.c. LSD was chosen as the control which was consistently included in each drug testing session. Apomorphine at the dose of 5 mg kg^{-1} s.c. was administered 20 min prior to LSD, while α-methyl-p-tyrosine (250 mg kg^{-1} i.p.) was injected 4 h before acute LSD challenge. L-DOPA (100 mg kg^{-1} i.p.) and carbidopa (25 mg kg^{-1} i.p.) were given 30 min before LSD. Naloxone (0.2 mg kg^{-1} s.c.) was administered both 30 min after and 5 min before LSD to two separate groups of animals. Furthermore, another group of rats were pre-treated with PLG (40 mg kg^{-1} s.c.) 30 min before LSD.

Another series of experiments was conducted to investigate the possible cholinergic involvement in LSD-induced catalepsy. Muscarinic antagonists, scopolamine (2 mg kg^{-1} i.p.) and atropine sulfate (30 mg kg^{-1} i.p.) were administered 20 min prior to LSD to separate groups of rats. On the other hand, the muscarinic agonist, pilocarpine (100 mg kg^{-1} i.p.) was injected 5 min prior to LSD and methylatropine (5 mg kg^{-1} i.p.) was given 5 min earlier to eliminate peripheral cholinomimetic behavioural effects. Nicotine at the dose of 5 mg kg^{-1} i.p. was injected 10 min prior to LSD while hexamethonium (5 mg kg^{-1} i.p.) was administered 5 min earlier to minimize peripheral nicotinic effects. Furthermore, another group of rats was pre-treated with mecamylamine (4 mg kg^{-1} s.c.) 10 min prior to LSD.

Statistics. The group mean of the catalepsy score was subjected to statistical analysis by the non-parametric Mann-Whitney *U*-test. All significant levels are two-tailed.

Results

Dose-Response Relationship of LSD-Induced Catalepsy. Within 5–10 min after subcutaneous LSD administration (50–500 μg kg^{-1}) the rats consistently and dose-dependently exhibited some elements of stereotypy including lateral head weaving, backward crawling and reciprocal forepaw treading. In addition, enhanced startle response to auditory and tactile stimuli was observed. After the initial phase of hyperexcitability lasting approximately 30 min was over, the animals remained relatively immobile, but not sedated and displayed sporadic whole-body twitch. The onset of catalepsy did not occur until 60 min after LSD administration. While LSD at the doses of 50 and 250 μg kg^{-1} did not produce any appreciable degree of

Table 1. Time course of dose-related LSD-induced catalepsy in rats

Doses of LSD	Catalepsy score[a] at various times (min) after LSD administration (s.c.)				
(μg kg^{-1})	30 min	60 min	90 min	120 min	180 min
500	3.8	37.2	80.5	103.6	74.3
375	4.0	31.5	71.5	67.2	10.6
250	3.4	4.6	18.4	25.5	19.5
50	2.9	13.6	11.3	24.9	29.0

[a] Values represent the mean of the cataleptic score obtained from at least 6–10 animals. Since the data were subjected to Mann Whitney *U*-test, it was considered unnecessary to render the S.E.M. For the 375 μg kg^{-1} LSD group, $n = 24$

Table 2. Effects of dopaminergic agents, naloxone and PLG on LSD-induced catalepsy

Drug treatments	Catalepsy score[a] at various times (min) after LSD administration (s.c.)					
	30 min	60 min	90 min	120 min	180 min	240 min
Control[a]	4.0	31.5	71.5	67.2	10.6	6.0
Apomorphine	2.7	5.6*	8.7**	25.6**	8.5	–
αMPT	4.7	34.3	53.2	63.7	61.5	10.0
L-DOPA	4.8	15.2	7.4**	6.6**	7.6	–
Naloxone (pre-)	11.2	69.0	95.4	88.4	75.2**	74.7**
Naloxone (post-)	10.4	11.6*	13.0**	9.8**	37.0	6.5
PLG	56.5	57.2	77.2	80.2	89.7**	93.3**

[a] All groups of rats (except naloxone) were pre-treated with the various agents at specific time intervals prior to acute challenge with LSD at the dose of 375 μg kg^{-1} s.c. The "naloxone (post-)" group was administered 30 min after LSD. The details of the dosage schedule were described in "Methods". Values represent the mean cataleptic score obtained from at least six animals. For the LSD-control group, $n = 24$

* Significantly different from LSD-control ($P < 0.05$) at the respective time interval

** Significantly different from LSD-control ($P < 0.01$) at the respective time interval

catalepsy, higher doses of LSD elicited cataleptic responses in a dose-dependent manner (Table 1). The intensity of the cataleptic response attained a maximum at 90–120 min and declined somewhat precipitously thereafter. The cataleptic effects of 500 μg kg^{-1} LSD extended well beyond the 3-h observation period. Higher doses of LSD, which would otherwise introduce extraneous behavioural effects, were not examined in our present study.

Equivalent dose of the non-hallucinogenic congener of LSD, 2-bromo-LSD (375 μg kg^{-1}) did not produce any biphasic behavioural effects typical of LSD (data not shown).

Effects of Dopaminergic Agents, Naloxone and PLG. The results of treatment with dopaminergic agents are presented in Table 2. It can be seen that αMPT (250 mg kg^{-1} i.p.), the dopamine depleting agent, when given 4 h prior to LSD, slightly prolonged LSD action. Pre-treatment with the dopamine agonist, apomorphine (5 mg kg^{-1}) significantly attenuated induced cataleptic effects at 60, 90 and 120 min. Similarly L-DOPA, the precursor of dopamine (100 mg kg^{-1} i.p.), administered 30 min after LSD in the presence of peripheral decarboxylase inhibitor, carbidopa (25 mg kg^{-1} i.p.) effectively reduced the intensity of LSD catalepsy. Equivalent doses of L-DOPA and apomorphine did not elicit any cataleptic responses (data not shown).

Naloxone, the narcotic antagonist, at the dose of 0.20 mg kg^{-1} s.c., prevented the development of the cataleptic response when administered 30 min following LSD injection. Conversely, pre-treatment with the identical dose of naloxone 5 min before LSD administration, shortened the initial hyperexcitable phase and significantly potentiated the cataleptic action of LSD. Pre-treatment with PLG (40 mg kg^{-1} s.c.) markedly potentiated the central effects of LSD. PLG and naloxone alone did not produce any cataleptic state.

Effects of Cholinergic Agonists and Antagonists. Table 3 demonstrates the influence of muscarinic and nicotinic agents on LSD-induced catalepsy. Whereas scopolamine, at the dosage of 2 mg kg^{-1} i.p., when administered 30 min prior to LSD, did not significantly modify the cataleptic behaviour, a higher dosage of scopolamine (10 mg kg^{-1}) intensified the initial excitable phase and consequently delayed the onset of the cataleptic reaction. The subsequent cataleptic response, however, was significantly prolonged and potentiated. Atropine (30 mg kg^{-1} i.p.) exerted similar, though much less potent, effects on LSD-induced catalepsy. The cholinergic modulation of LSD-induced catalepsy is likely to be central in origin, as equivalent dosage of methylscopolamine (10 mg kg^{-1}), the muscarinic antagonist incapable of crossing the blood-brain barrier, failed to alter LSD effects. No cataleptic behaviour was observed with equivalent doses of atropine and scopolamine (data not shown).

Pilocarpine (100 mg kg^{-1} s.c.) the muscarinic agonist, reduced the intensity of LSD-induced catalepsy at 60 and 90 min, although when administered alone elicited consistent catalepsy. In these experiments, we employed pre-treatment with methylatropine (5 mg kg^{-1} i.p.) to eliminate the peripheral cholinomimetic effects of pilocarpine, and hence any observed behavioural interactions of LSD with pilocarpine are likely to be central in origin.

Mecamylamine, the nicotinic antagonist, at the dose of 4 mg kg^{-1} s.c., significantly attenuated the LSD-induced cataleptic response at 90 min. Nicotine (5 mg kg^{-1} i.p.) prolonged the cataleptic action of LSD in the hexamethonium-protected group, without affect-

Table 3. Effects of muscarinic and nicotinic cholinergic agents on LSD-induced catalepsy

Drug pretreatment	Catalepsy score[a] at various times (min) after LSD administration (s.c.)					
	30 min	60 min	90 min	120 min	180 min	240 min
LSD-control[a]	4.0	31.5	71.5	67.2	10.6	6.0
Scopolamine[b]	3.0	3.0**	95.0	68.1	32.5	16.4
Scopolamine[c]	3.0	3.0**	3.7*	95.7	90.0**	54.3**
Atropine	3.0	3.0**	3.8*	6.6**	63.7*	30.1*
Pilocarpine	10.7	6.6	8.6	29.8	25.3	30.3
Pilocarpine (control)	5.6	12.6	16.6	35.4	30.0	26.7
Nicotine	4.0	24.6	46.7	57.2	56.2	42.4
Nicotine (control)	3.3	8.0	8.1	13.0	16.0	11.2
Mecamylamine	3.0	7.4	7.4**	29.0	16.2	13.6

[a] All groups of rats (except nicotine and pilocarpine control) were pretreated with various cholinergic agonists and antagonists at specific time intervals prior to acute challenge of LSD at the dose of 375 μg kg^{-1} s.c. Values represents the mean cataleptic score from at least six animals. For details, see "Method", $n = 24$

[b] Scopolamine (2 mg kg^{-1} i.p.)

[c] Scopolamine (10 mg kg^{-1} i.p.)

* Significantly different from LSD-control ($P < 0.05$) at the respective time interval

** Significantly different from LSD-control ($P < 0.01$) at the respective time interval

ing the intensity of the cataleptic response throughout the experiment. Mecamylamine alone did not produce any marked behavioural effects.

Discussion

The results of our study demonstrate that dopaminergic and cholinergic drugs differentially modify the cataleptic effect of LSD. It is apparent that LSD catalepsy may not be mediated primarily by competitive blockade of post-synaptic striatal dopamine receptors in a manner analogous to that exerted by cataleptogenic neuroleptics, inasmuch as its derivative BOL, while failing to produce any cataleptic reaction in our hands, was equally potent in enhancing dopamine turnover (Persson, 1977b). It appears likely that the behavioural syndrome may be ascribed to a presynaptic receptor-mediated event. Using the in vivo model developed by Walters and Roth (1976) for presynaptic dopamine receptor, Persson (1977a) found that both apomorphine and LSD inhibited the γ-butyrolacetone-induced increase in L-DOPA (3,4-dihydroxyphenylalanine) accumulation in the striatum and that BOL antagonized the biochemical effects of the latter. Hence the biochemical data may be interpreted to suggest that LSD preferentially activates the "auto-inhibitory" presynaptic dopamine receptor regulating dopamine synthesis and release as originally hypothesized by Carlsson et al. (1972). The cataleptic response may be considered the behavioural expression of the consequent attenuation of the nigro-striatal dopaminergic neurotransmission. In support of our contention, low dose of the dopamine agonist, piribedil, significantly potentiated haloperidol-induced catalepsy (Fadda et al., 1975) and exacerbated the extrapyramidal side effects of haloperidol in humans (Corsini et al., 1978). However, the presumed action of LSD on presynaptic dopamine receptor was partially antagonized by post-synaptic receptor stimulation induced by high dose of apomorphine as well as by dopamine precursor loading.

The cataleptic state induced by LSD would be essentially incompatible with the claim for its dopaminergic agonist properties (Christoph et al., 1977; Trulson et al., 1977). It should be emphasized, however, that the manifestation of agonist/antagonist properties of LSD may depend on the functional state of the receptor in vivo. If the post-synaptic dopamine receptor is rendered supersensitive by pharmacologically-induced deprivation of its normal endogenous substrate, LSD may function as an agonist. Under normal conditions, LSD may behave as a pre-synaptic agonist and a partial post-synaptic antagonist. The paradoxical mixed agonist-antagonist properties of LSD probably explains the failure to observe any change in dopamine receptor sensitivity upon chronic administration (Trulson et al., 1979), despite the concurrent depletion of dopamine (Peters and Tang, 1977).

Our finding that stimulation of central muscarinic receptor achieved with pilocarpine attenuated LSD-induced catalepsy while anti-muscarinic agents such as scopolamine enhanced LSD behavioural effects, may be interpreted to suggest that LSD catalepsy is mediated through inhibition of cholinergic neuronal activity. It is difficult, however, to reconcile this interpretation with the established view of mutually

antagonistic dopaminergic-cholinergic functional relationships within the nigro-striatal system regulating motor function (Klawans, 1973). The scheme of dopaminergic-cholinergic equilibrium, albeit valid, is perhaps somewhat simplistic, in view of recent evidence delegating direct synaptic role to acetylcholine in facilitating the release of striatal dopamine (Giorguieff et al., 1976). It may be argued, however, that muscarinic receptor blockade by scopolamine only delayed the onset of the cataleptic response and that the later enhanced cataleptic effect represents a non-specific rebound phenomenon. It is possible that LSD has exerted maximal inhibition on the activity of cholinergic neurons and that further administration of anticholinergic agents may fail to superimpose additional behavioural effects. It is not known whether LSD causes a decline in acetylcholine turnover in the striatum and other brain regions, and the extent to which such postulated neurochemical change is related to the repertoire of behavioural changes. On the other hand, it is not surprising that central nicotinic receptor activation by nicotine only slighly prolonged LSD-induced catalepsy, since immunofluorescence studies revealed a paucity of nicotinic binding sites as labelled as α-bungarotoxin in the striatum (Amenta et al., 1979). Besides, the observed slight antagonism by mecamylamine should be interpreted with caution, as this agent does not function as a typical nicotinic antagonist in α-bungarotoxin binding studies (Morley et al., 1977).

Although analysis of net effects of cholinergic manipulations of LSD-induced catalepsy by systemic administration of agonists and antagonists fails to identify the exact neuroanatomical foci, the pattern of drug effects raises the intriguing possibility that LSD may interact with extrastriatal sites. Non-dopaminergic efferent pathway arising from the pars reticulata of the substantia nigra (DiChiara et al., 1977), and the nucleus accumbens, the terminal of the mesolimbic dopaminergic pathway, are likely candidates in this regard.

The profile of the LSD-induced behavioural responses towards cholinergic modulation bears remarkable similarities to morphine – (Kaakkola and Ahtee, 1977) and methadone-induced catalepsy (Ahtee, 1976), but diverges significantly from neuroleptic-induced catalepsy in an opposite fashion (Ezrin-Waters et al., 1976). In our present study, we have confirmed the results of the recent investigation demonstrating the reversal effect of the narcotic antagonist, naloxone, on LSD catalepsy (Fertnizer and Fischer, 1978). The effect of LSD is probably not mediated through direct opiate agonist activity, but may occur indirectly through the release of enkephalins activating the naloxone-sensitive opiate receptors which in turn modulate dopaminergic activity. It is difficult, however, to reconcile the possible enkephalin-releasing action of LSD with the demonstrated antagonism by LSD of stimulation-induced analgesia (Hayes et al., 1977). Alternatively, the release of endogenous opioid peptides is regulated by a local negative feedback loop operating at the pre-synaptic level.

The hypothesized LSD-enkephalin interaction in our behavioural model is more complex than envisaged, since pre-treatment with naloxone potentiated the development of the cataleptic effect. Naloxone may synergise with LSD in eliciting the release of enkephalins; the latter explanation has been advanced for naloxone-induced analgesia in humans (Levine et al., 1979).

On the other hand, the paradoxical marked potentiation of LSD-induced catalepsy by post-treatment with PLG, the potential anti-Parkinsonian agent (Plotnikoff and Kastin, 1976) may be tentatively explained in terms of complex interaction with a pharmacologically distinct peptide receptor. Previous studies indicate that PLG exerted significant antagonistic activity against fluphenazine (Voith, 1978) and morphine – (Chiu and Mishra, 1979) catalepsy. The ultimate significance of LSD-PLG and morphine-PLG interactions at the behavioural level, however, may only be realized by successful identification and characterization of the postulated PLG receptor.

In summary, whatever the exact neuronal circuitry involved, the cataleptic response elicited by LSD may be mediated through diminished dopaminergic activity. It would be tempting to speculate that LSD differentially activates pre-synaptic auto-inhibitory dopamine receptor. Cholinergic manipulation of LSD effects suggests that LSD may indirectly inhibit net cholinergic activity at some extrastriatal site. Enkephalins seem to modulate LSD action through some yet unidentified mechanism. In the final analysis, it is possible that concomitant changes in the pharmacokinetic processes of distribution and metabolism may explain the differential interaction of LSD with dopaminergic and cholinergic agents. Nevertheless, the behavioural profile of LSD is equally consistent with our postulated function interaction of LSD with dopaminergic and cholinergic neuronal systems.

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