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THE DISCRIMINATIVE STIMULUS PROPERTIES OF LSD: MECHANISMS OF ACTION*

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Summary—The CNS correlates of D-lysergic acid diethylamide (LSD) actions were investigated by means of a sensitive and specific behavioural assay procedure. Rats were trained to discriminate D-LSD from saline in two lever operant chambers. After intraperitoneal injections of 0.08 mg/kg of LSD, reinforcement could be obtained only by responding on one particular lever (left or right); responding on the opposite lever was reinforced only after saline injections. Once the LSD and saline exerted reliable stimulus control over lever choice (85% correct), rats were tested with various agents which alter the functional activity of the transmitter-containing neuronal systems. L-Tryptophan, chlorimipramine and fluoxetine, all of which increase the synaptic availability of serotonin, neither blocked nor, by themselves, mimicked (transferred to) LSD. However, quipazine, a putative serotonin agonist, produced an almost complete (78%) transfer to LSD. The presumed serotonin antagonists: methiothepin, 2-bromo-D-lysergic acid diethylamide, methysergide, cyproheptadine and cinanserin, blocked the LSD cue in a dose-related manner. The potent dopamine antagonists: haloperidol, fluphenazine, trifluoperazine, α-flupenthixol, and (+)-butaclamol, were without effect on the discriminability of LSD as were α- and β-adrenergic, cholinergic and histaminergic antagonists. Apomorphine, a dopamine agonist, produced a partial transfer to LSD. These data indicate that the discriminative stimulus properties of LSD may be mediated by post-synaptic serotonin or LSD receptors. Dopamine receptors did not seem to be involved in the LSD stimulus cue.

The mechanisms underlying the spectrum of effects produced by the potent hallucinogen LSD remain obscure. For some time, behavioural, biochemical and electrophysiological evidence has pointed to the serotonergic (5-HT) neuronal system as the primary, if not the exclusive, site of LSD action in brain. More recently, direct binding experiments have demonstrated that LSD interacts with both 5-HT (Bennet and Snyder, 1975, 1976; Snyder and Bennet, 1975) and dopamine (DA) receptors (Burt, Creese and Snyder, 1976; Creese, Burt and Snyder, 1975a, b). A high-affinity, stereospecific receptor site for D-LSD itself has also been described (Lovell and Freedman, 1976).

In view of the several proposed mechanisms of action of LSD, the confirmed interactions of this hallucinogen with neurotransmitter receptors at a biochemical level, and the need for further assessment of the role these interactions play in mediating the behavioural effects of LSD, it was decided to investigate the neurochemical correlates of the discriminative stimulus properties of LSD (Cameron and Appel, 1973) in some detail. In contrast to other behavioural techniques in which the effect of a drug on the frequency of some behaviour (e.g. response rate, locomotor activity) is typically observed, the measurement of the stimulus properties of drugs is unique in that the drug effect (stimulus) is studied directly. Further, the LSD cue is quite specific in that it can be mimicked by only a few other pharmacologically similar compounds such as psilocybin and mescaline (Cameron and Appel, 1973; Kuhn, White and Appel, 1977). Most importantly, since rats can reliably discriminate doses of LSD as low as 0.005 mg/kg (Greenberg, Kuhn and Appel, 1975), this technique is one of the most sensitive behavioural assays of LSD thus far reported in this species.

METHODS

Subjects

Thirty-six male albino rats (Sprague–Dawley) approximately 90 days old and weighing 250–300 g at the start of the experiment were used. The animals were housed individually in a room of constant temperature (22°C) and humidity (40–50%) and maintained on a 14 hr light–10 hr dark cycle.

Apparatus

Four commercially available experimental chambers contained in sound-proof, ventilated enclosures were used (BRS/LVE Model No. 143–24). Each box

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contained two levers on the front panel separated by a liquid feeder which delivered 0.01 ml of water. Boxes were illuminated by a 28 V white house light. Electromechanical programming and recording equipment was located in an adjacent room.

Discrimination training

With slight modifications, the procedure is the same as that previously described (Kuhn, Appel and Greenberg, 1974; Kuhn, Greenberg and Appel, 1976). Rats were trained to discriminate 0.08 mg/kg of LSD from saline. After reducing body weight to 80% of *ad libitum* by restricting water intake, animals were shaped to bar-press on a fixed ratio 1 (FR 1) schedule (each bar-press was followed by 0.01 ml of tap water). During initial training only one lever was present. In an effort to enhance the rate of acquisition of the drug discrimination, rats were given injections concurrent with behavioural training. Thus, on Day 1 animals were injected with saline and, 15 min later, trained to bar-press on one lever ("saline" lever) for 60 min. The same treatment was given on Day 2: the schedule of reinforcement was gradually increased from FR 1 to FR 32. On Day 3 rats were injected with 0.08 mg/kg of LSD and, 15 min later, placed in the chamber with the opposite lever ("LSD") present. To control for possible position preferences, the LSD lever was the left lever for half of the rats and the right lever for the other half. Training continued on the LSD lever for 2 days.

Behavioural training and injections continued on a double alternation sequence until rats received 4 days on the LSD lever alone and 4 days on the saline lever alone. This amount of training was sufficient for all rats to reach high rates of responding on FR 32 on each lever. On Day 9, and on each day throughout the rest of the experiment, rats were injected and placed in the operant chambers for 30 min with both levers present. Responding on the "correct" lever (LSD or saline lever, depending on the injection) was reinforced on an FR 32 schedule of reinforcement. Incorrect responding had no programmed consequences. Discrimination training continued until all rats responded on the lever appropriate for the injection, greater than 90% correct (see below).

Tests with 5-HT agonists and antagonists

Once the LSD and saline injections exerted reliable control over choice responding, test treatments were begun. The following 5-HT "agonists" were given both alone and, except for quipazine, in combination with LSD at the indicated intervals before testing for lever choice: 100 mg/kg of L-tryptophan (TRY: 30 or 120 min), 5.0 mg/kg of chlorimipramine (CMI: 60 min), 10.0 mg/kg of fluoxetine (Lilly 110140: 240 min) and 2.5 mg/kg of quipazine. These dose and time parameters (except TRY: 120 min) were chosen on the basis of pharmacological and electrophysiological data which show that TRY (Gallager and Aghajanian, 1976; Trulson and Jacobs, 1976), CMI (Gallager and Aghajanian, 1975) and fluoxetine (Fuller, Perry and Molloy, 1974) produce profound depression of both raphe unit activity and 5-HT uptake. L-Tryptophan was also tested at 120 min, a time when the *in vivo* release of 5-HT is maximal after TRY loading (Terneaux, Boireau, Bourgoin, Hamon, Hery and Glowinski, 1976). The animals were placed in the chambers for testing 15 min after LSD. However, to avoid confounding the results with additional learning, reinforcement was withheld (extinction) on all test days. Rats were removed from the chambers immediately upon completing 32 responses on one lever or the other, or after 15 min in those cases where a test drug had a depressant effect on response rate.

The putative 5-HT antagonists methiothepin (MTP), cyproheptadine (CYP), methysergide (UML), 2-bromo-D-lysergic acid diethylamide (BOL) and cinanserin (CIN) were also tested as antagonists of LSD (see Fig. 1 for doses). Each drug, except BOL, was injected 60 min prior to LSD; BOL was injected 15 min before LSD. Test treatments were given in random order to one of 3 separate groups of rats ($N = 12$/group) which were discriminating LSD from saline. In order to minimize possible differential sensitivity to the antagonists between groups, the same group was tested with all doses of a particular antagonist.

Tests with DA agonists and antagonists

Different groups of rats were tested for lever choice 15 min after injections of 0.5 or 1.0 mg/kg of apomorphine. The DA antagonists haloperidol, fluphenazine, trifluoperazine, α-flupenthixol and (+)-butaclamol were injected 60 min prior to LSD (Table 2); rats were tested for lever choice 15 min after LSD. These compounds were chosen both because they are the most potent DA antagonists in several different assay systems (Clement-Cormier, Kebabian, Petzold and Greengard, 1974; Creese *et al.*, 1975a, b; Seeman, Chau-Wong, Tedesco and Wong, 1975) and because they are representative of the different chemical classes of DA antagonists (butyrophenone, phenothiozine, thiothixene, benzocylcoheptapyridoisoquinolinol). It was necessary to test a variety of DA antagonists to avoid the possibility that some structural characteristic specific to one class, in addition to those characteristics responsible for DA antagonism, would produce antagonism of the LSD cue.

Tests with other drugs

Finally, the α- and β-adrenergic antagonists phentolamine (10 mg/kg) and propranalol (20 mg/kg), respectively, the anticholinergic atropine (2 mg/kg) and the antihistaminic promethazine (3.0 mg/kg) were tested as antagonists of LSD. Each drug was injected 60 min before LSD.

Drugs. Doses of the following drugs were based on the weight of the free acid or base: methiothepin maleate, BOL tartrate, methysergide maleate, cyproheptadine HCl, cinanserin HCl, haloperidol, trifluo-

Table 1. Effects of 5-HT agonists and antagonists on lever choice in rats trained to discriminate LSD from saline

Pretreatment	Dose (mg/kg)	Test drug	Dose (mg/kg)	Injection test[a] interval (min)	% LSD[b] response
		LSD	0.08	15	94 ± 2
		Saline		15	3 ± 2
		TRY	100.0	30	36 ± 3[c]
		TRY	100.0	120	37 ± 5[c]
		CMI	5.0	30	3 ± 1[c]
		Fluoxetine	10.0	240	20 ± 3[c]
		Quipazine	2.5	15	78 ± 2[d]
TRY	100.0	LSD	0.08	30	94 ± 1[d]
CMI	5.0	LSD	0.08	60	92 ± 1[d]
Fluoxetine	10.0	LSD	0.08	240	95 ± 1[d]

[a] This interval refers to the time between injection of drugs (other than LSD) and testing. Testing was always carried out 15 min after LSD.
[b] Mean of 12 observations (± S.E.M.).
[c] Not significantly different from saline control.
[d] Not significantly different from LSD control.

perazine HCl, (+)-butaclamol HCl, α-flupenthixol HCl, fluphenazine 2HCl, L-tryptophan methyl ester HCl, promethazine HCl. Doses of the following drugs were based on the weight of the salt: chlorimipramine HCl, phentolamine HCl, propranalol HCl, fluoxetine, atropine sulphate, quipazine maleate, apomorphine HCl, D-amphetamine sulphate and D-LSD tartrate. Cyproheptadine was prepared for injection by dissolution in 15% aqueous propylene glycol. Haloperidol was dissolved in a minimal volume of lactic acid and diluted with distilled H_2O containing 0.5 mg methylparaben and 0.05 mg propylparaben per milliliter. Apomorphine was dissolved in 0.2% ascorbic acid. All other drugs were dissolved in 0.9% NaCl. Except for LSD, all drugs were prepared fresh, immediately before use. All injections were given intraperitoneally.

Data analysis

Data are expressed as the percentage of extinction responding on the LSD lever: the number of "drug appropriate responses" divided by the total number of responses on both levers. Since the dependent variable is a proportion, raw data were subjected to an arcsin square root transformation (Winer, 1962) and statistical analyses (below) were carried out on these transformed data.

RESULTS

All animals acquired the LSD-saline discrimination fairly rapidly; lever choice reached 90% correct (following both LSD and saline) after 12–15 days of training. Nevertheless, testing with potential agonists and antagonists was not begun until training continued for more than 45 days.

Tests with 5-HT agonists and antagonists

The results of both transfer and antagonism tests with TRY, CMI, fluoxetine and quipazine are shown in Table 1. It can be seen that after injections of TRY, CMI, and fluoxetine (alone), response choice was primarily on the saline lever. Although TRY (both time intervals) produced 36% and fluoxetine produced 20% responding on the LSD lever, these values were not significantly different from the saline control (planned comparisons *t*-test). The only drug to produce a significant transfer to LSD was quipazine, which resulted in 78% responding on the LSD lever. L-Tryptophan, CMI and fluoxetine, when injected before LSD, did not reduce (block) the discriminability of LSD.

The results of tests with the putative 5-HT antagonists are presented in Figure 1. It is apparent that each drug reversed the LSD cue in a dose-related fashion. Simple one-way analyses of variance (repeated measures) of individual dose–response curves indicated that the MTP ($P < 0.01$), CYP ($P < 0.01$), UML ($P < 0.01$) and CIN ($P < 0.01$) dose effects (antagonism) were significant. However, the BOL curve did not quite reach significance. It should be noted that only two doses of BOL and CIN were tested because of the limited available quantities of these drugs. The most potent antagonist of the LSD cue was MTP which produced antagonism at doses as low as 0.10 mg/kg (0.28 μmol/kg); CYP was also quite potent.

Tests with DA agonists and antagonists

The results of tests with DA agents are presented in Table 2. Apomorphine, at 0.5 and 1.0 mg/kg, produced 46.0 and 56.0% responding, respectively, on the LSD lever. These values were significantly different ($P < 0.05$) from both LSD and saline controls. Not one DA antagonist had any effect on the discriminability of LSD. Since these doses of at least haloperidol (Schechter and Cook, 1975), fluphenazine and α-flupenthixol are large enough to reverse significantly the stimulus properties of apomorphine (unpublished observations), there is little doubt that they were blocking DA receptors. Nevertheless, they did not

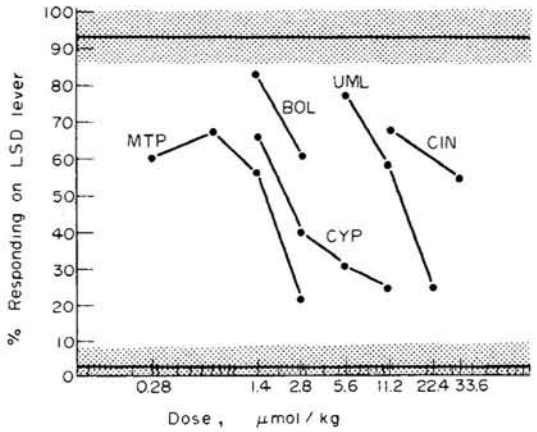

Fig. 1. Effects of presumed 5-HT antagonists on the discriminability of LSD. Each antagonist, except BOL, was injected 60 min before LSD: BOL was injected 15 min prior to LSD. Rats were always tested 15 min after LSD in extinction. The shaded areas at the top and bottom of the ordinate represent the ranges of lever choice on control LSD and saline days, respectively. Each point represents the mean of 12 rats. The ordinate is the per cent of total responding on the LSD lever after test treatments; abscissa —log dose of antagonists.

block LSD. Additional tests with α- and β-adrenergic blockers (phentolamine and propranalol), as well as an anticholinergic (atropine) and an antihistaminic (promethazine) demonstrated that these compounds were also without effect on the LSD stimulus cue; i.e. responding was completely on the LSD lever (data not shown).

DISCUSSION

The results of treatments with 5-HT agonists and antagonists may, at first, appear somewhat contradictory, i.e. 5-HT antagonists blocked but 5-HT agonists (with the exception of quipazine) did not mimic the LSD cue. There is conclusive biochemical evidence demonstrating that MTP, CYP, CIN, UML and BOL can block postsynaptic 5-HT receptors (Bennet and Snyder, 1975, 1976) leading to the obvious conclusion that LSD produces its discriminable cue by activating 5-HT receptors. In agreement with this, Browne and Ho (1975) found that the mescaline discriminative stimulus, which is similar to LSD (Hirschhorn and Winter, 1971; Cameron and Appel, 1973), is also antagonized by at least UML, CYP and CIN. It is not clear why Hirschhorn and Rosecrans (1974) were unable to block the LSD cue with CIN or CYP. Despite equally compelling evidence demonstrating that TRY (Gallager and Aghajanian, 1976; Trulson and Jacobs, 1976), CMI (Gallager and Aghajanian, 1975) and fluoxetine (Fuller and Steinberg, 1976) increase the synaptic (and receptor) availability of 5-HT, these "indirect" 5-HT agonists do not transfer to LSD.

These discrepant results can be reconciled by either of two different explanations. First, LSD may be acting on postsynaptic 5-HT receptors whereas TRY, CMI and fluoxetine induce their primary neurochemical effects by acting on presynaptic processes (release or uptake inhibition). However, it remains to be demonstrated that the present behavioural assay can distinguish between these different sites of drug action.

Second, LSD may be acting at sites which are distinct from postsynaptic 5-HT receptors. Lovell and Freedman (1976) and Bennet and Snyder (1975) recently described a specific binding site for LSD in rat brain. Like the LSD discriminative stimulus (Cameron and Appel, 1973), this LSD receptor is selective for the D-stereoisomer. However, 5-HT is not a very potent agonist at the LSD receptor (Lovell and Freedman, 1976; Bennet and Snyder, 1975). The

Table 2. Effects of DA agonists and antagonists on lever choice in rats trained to discriminate LSD from saline

Pretreatment	Dose (μmol/kg)	Test drug	Dose (mg/kg)	Injection test interval (min)	% LSD[a] response
		LSD	0.08	15	93 ± 2
		Saline		15	4 ± 1
		Apomorphine	0.05	15	46 ± 6[b]
		Apomorphine	1.0	15	56 ± 7[b]
Haloperidol	0.7	LSD	0.08	60	94 ± 2
	1.4	LSD	0.08	60	92 ± 2
Fluphenazine	2.8	LSD	0.08	60	95 ± 7
	5.6	LSD	0.08	60	93 ± 9
Trifluperazine	1.4	LSD	0.08	60	97 ± 1
	2.8	LSD	0.08	60	95 ± 1
	5.6	LSD	0.08	60	99 ± 1
α-Flupenthixol	0.7	LSD	0.08	60	98 ± 4
	1.4	LSD	0.08	60	100
(+)-Butaclamol	0.7	LSD	0.08	60	98 ± 4
	1.4	LSD	0.08	60	100

[a] Mean of 12 observations (± S.E.M.) except for α-flupenthixol and (+)-butaclamol, where $N = 6$.

[b] Significantly different from both LSD and saline control.

putative 5-HT antagonists were actually found to be more potent antagonists of LSD than of 5-HT binding (Bennet and Snyder, 1976) and the order of potency of these agents as antagonists of the LSD discriminative stimulus (MTP > CYP > BOL > UML > CIN; Fig. 1) corresponds, perhaps, more closely with their order of potency as antagonists of LSD binding (MTP ⩾ BOL > UML > CYP > CIN; Lovell and Freedman, 1976) than with their potency as 5-HT receptor antagonists (BOL > UML = MTP > CYP; Bennet and Snyder, 1976)—facts which suggest that the LSD and 5-HT receptor sites, while probably related, are not identical.

These neurochemical data are in agreement with the results shown in Figure 1. In addition, they establish that while the 5-HT antagonists block *both* LSD and 5-HT receptors, as well as the LSD cue, 5-HT will not transfer completely to LSD since it is not an agonist at the LSD receptor. Conversely, since LSD is a potent agonist at 5-HT receptors (Bennet and Snyder, 1975, 1976), it can mimic certain "5-HT-mediated" effects including the stimulus properties (Hirschhorn, Hayes and Rosecrans, 1975) and the inhibitory influence of 5-HT (both effects induced by electrical stimulation of the dorsal raphe nucleus) on habituation to startle—eliciting auditory stimuli (Sheard and Aghajanian, 1968).

The transfer to LSD produced by quipazine is not inconsistent with the preceding discussion. Although quipazine may act as an agonist at 5-HT receptors (Green, Youdim and Grahame-Smith, 1976; White, Kuhn and Appel, 1977), the discriminable similarity between LSD and quipazine may be based, instead, on a structural relationship between these two drugs (i.e. the quinoline ring system) which is exclusive of a similarity to the basic 5-HT (indole) moiety. Another observation establishes that quipazine is acting directly to mimic LSD, not indirectly by inhibiting 5-HT uptake: CMI and fluoxetine, both of which are far more potent than quipazine as *in vivo* 5-HT uptake inhibitors, do not transfer to LSD.

Thus, quipazine is now one of very few drugs capable of transferring to LSD. Although it is not always true that the discriminable similarity between two drugs in rats predicts subjective (hallucinogenic) similarity in man (Kuhn *et al.*, 1977), the recent demonstration that LSD also transfers to quipazine and the extent to which this symmetrical transfer occurs (White *et al.*, 1977) suggests that the potential untoward effects of quipazine outweigh the possible therapeutic use of this agent as an antidepressant (Rodriguez and Pardo, 1971).

The results of test treatments with DA agonists and antagonists do not indicate a prominent role for DA receptors in mediating the stimulus properties of LSD. A variety of potent DA receptor antagonists had no effect on the discriminability of LSD. In view of these findings and for reasons listed below, the partial apomorphine transfer (56%) to LSD, by itself, is not convincing evidence to the contrary. (1) A dose of apomorphine (1.0 mg/kg) approximately 15 times larger than the dose of LSD (0.08 mg/kg) produced just a partial transfer whereas, on the basis of receptor binding studies which demonstrated that apomorphine has a greater affinity for the DA receptor than LSD (Creese *et al.*, 1975b), a complete transfer would be predicted. (2) Apomorphine can displace LSD from its binding sites in the hippocampus, a brain structure apparently devoid of DA receptors (Burt *et al.*, 1976). (3) Amphetamine, another DA agonist, does not transfer to LSD (Cameron and Appel, 1973; Schechter and Rosecrans, 1972). Taken together, these results indicate that LSD and apomorphine can interact, even at a behavioural level, on the basis of a similarity apart from agonistic effects at DA receptors.

The present results do not agree with recent behavioural experiments which purport DA agonistic effects by LSD (Dixon, 1968; Fog, 1969; Kelley, 1975; Kelley and Iversen, 1975; Pieri, Pieri and Haefely, 1974; Pieri, Pieri, Saner, DaPrada and Haefely, 1975). Unfortunately, the results of these studies are difficult to interpret for two reasons. First, LSD produces 'stereotypy' at doses ranging from 5.0–10.0 mg/kg (Dixon, 1968; Fog, 1969). However, the present authors never observed DA-like stereotypy after LSD even at similar massive (toxic?) doses (Kuhn and Appel, 1975). Moreover, the descriptions of this LSD-induced stereotypy are more reminiscent of a 5-HT mediated myoclonic syndrome (Kuhn and Appel, 1975; Trulson, Ross and Jacobs, 1976) than of a DA-mediated syndrome. Second, the remaining behavioural demonstrations of a DA-like effect by LSD have been in rats with 6-OHDA lesions of the central DA neuronal systems (Kelley, 1975; Kelley and Iversen, 1975; Pieri *et al.*, 1974, 1975). Therefore, LSD must be acting on supersensitive and, perhaps, non-selective DA receptors (Costall, Naylor and Pycock, 1976; Ungerstedt, Ljungberg, Hoffer and Siggins, 1975). In addition, LSD-induced circling in animals with unilateral 6-OHDA lesions has not always been reproduced (Milson and Pycock, 1976; Pycock and Anlezark, 1975).

In summary, the discriminative stimulus properties associated with LSD represent a pharmacologically specific effect as evidenced by the present results as well as others (see Kuhn *et al.*, 1977). On the basis of antagonism studies (Fig. 1) and related biochemical experiments (Bennet and Snyder, 1975, 1976; Lovell and Freedman, 1976) it is concluded that the LSD stimulus cue is one behavioural manifestation of the interaction of LSD with postsynaptic 5-HT or, possibly, LSD receptors. This behavioural assay is also quite sensitive since other assay models detect postsynaptic 5-HT effects by LSD only at very high doses (Kuhn and Appel, 1975; Trulson *et al.*, 1976). Recent electrophysiological studies have indicated that LSD acts selectively on presynaptic 5-HT neurons, i.e. the dorsal raphe nuclei (Aghajanian, Haigler and Bennet,

1975). However, the descriptions of high affinity receptor sites for 5-HT and LSD which are associated with post-synaptic neuronal membranes and which are blocked by MTP and other 5-HT antagonists (Bennet and Snyder, 1975, 1976; Lovell and Freedman, 1976), when considered with the present behavioural results, indicate that the interaction of LSD with such postsynaptic receptors must also be an important aspect of the mechanism of action of this potent hallucinogen.

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