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Training Dose as a Factor in LSD-Saline Discrimination

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Abstract. To assess the effects of training dose on the discriminative stimulus properties of LSD, groups of rats (eight/group) were trained to discriminate each of three doses of LSD (0.02, 0.08 or 0.32 mg/kg) from saline. This was accomplished by using a method of progressively altering dose ("fading"). Dose-response tests revealed that the three LSD cues were specific to the dose used during training and that, as the training dose declined, the slope of the LSD dose-response curve became less steep. Substitution tests with direct serotonin (5-HT) agonists (quipazine, MK-212, 5-methoxy-N,N-dimethyltryptamine) and antagonism tests with central 5-HT antagonists (methiothepin and cyproheptadine) indicated that 5-HT is involved in mediating the in vivo effects of LSD and that training dose co-determines (along with the dose of the test compound) the extent of substitution or antagonism. In addition, substitution tests with the peripherally-active 5-HT agonist 5-methoxytryptamine and 5-HT antagonist xylamidine suggested that the peripheral serotonergic actions of LSD may be involved (in part) in the low dose (0.02 mg/kg) LSD cue. In contrast to 5-HT, dopamine (DA) did not appear to be involved in the discriminative stimulus properties of LSD, because no significant dose or group effects were seen during tests with the DA agonists apomorphine and *d*-amphetamine or the DA antagonist haloperidol.

Key words: LSD – Drug discrimination – Training dose – Serotonin – Dopamine

Substitution and antagonism tests following drug discrimination (DD) training have been used with considerable success, both to predict agents that might produce similar subjective effects in humans and to analyze neuronal mechanisms underlying such effects (Colpaert and Rosecrans 1978). Such tests indicate that serotonergic (5-HT) neuronal systems are involved preferentially, if not exclusively, in the effects of lysergic acid diethylamide (LSD) in vivo (Kuhn et al. 1978; Rosecrans and Glennon 1979). This result does not agree entirely with those derived from experiments employing other behaviors such as drug-induced locomotion (Kelley and Iversen 1975), stereotypy (Fog 1969) and circling (Pieri et al. 1974), which suggest that agonistic actions of LSD at dopamine (DA) receptors also play a prominent role in mediating the behavioral effects of this compound. Since DD experiments typically employ relatively low doses of LSD (0.08 – 0.12 mg/kg) (Cameron and Appel 1975; Hirschhorn und Rosecrans 1974; Kuhn et al. 1978; Rosecrans and Glennon 1979; White et al. 1980) as compared to those that elicit behaviors characteristic of DA agonists (0.2 – 5.0 mg/kg), it is possible that LSD activates DA receptors only at high doses. Since training dose can determine the results of substitution and antagonism tests with other compounds such as opiates (Colpaert et al. 1980a, b; Jarbe and Rollenhagen 1978; Shannon and Holtzman 1979; Teal and Holtzman 1980) we reasoned that the apparent lack of DA involvement in the LSD cue may be due to the relatively low doses that have been studied.

To assess the effects of training dose on the discriminative stimulus properties of LSD and, in particular, the relative roles of 5-HT and DA in mediating these properties, groups of rats were trained to discriminate three different doses of LSD (0.02, 0.08 and 0.32 mg/kg) from saline. To accomplish this, a previously-reported (Colpaert et al. 1980a; Overton 1979) "fading" procedure (progressively decreasing dose) was used to obtain the discrimination of a low dose of LSD (0.02 mg/kg) and a new variant of fading (progressively increasing dose) was used to obtain the discrimination of a high dose (0.32 mg/kg); without these progressive alterations the low dose is discriminated poorly (Cameron and Appel 1973) and the high dose is so behaviorally disruptive that adequate rates of lever-pressing are never obtained (pilot data). After the rats acquired these discriminations, they were given: (1) dose-response tests with LSD, (2) substitution tests with 5-HT and DA agonists and (3) antagonism tests with 5-HT and DA antagonists.

Materials and Methods

Subjects

Twenty-four experimentally-naive male albino rats (Sprague-Dawley) were used. Each animal was approximately 90 days old and weighed 280 – 320 g at the beginning of the experiment. They were maintained at 80 – 85% of their expected free-feeding weight by restricting water intake to that received during experimental sessions, a 10-min exposure following each session and 6 – 12 h of freely-available water once a week. They were housed individually in a room of constant temperature (21 – 23 C) and humidity (40 – 50%) maintained on a 12-h light-dark cycle (7:00 a.m. – 7:00 p.m.).

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Apparatus

Eight commercially-available operant chambers (BRS/LVE Model No. 143–24), housed in light- and sound-attenuating shells, located in two rooms designated for testing (four/room) were used throughout the experiment. Each box contained two levers separated by a dipper which supplied 0.1 ml tap water as reinforcement. Programming and recording of data were controlled by electromechanical and solid-state equipment located in an adjacent room.

Procedure

Shaping. Subjects were injected intraperitoneally (IP) once a day with either LSD (0.08 mg/kg) or sterile saline (0.9% NaCl) and placed in experimental chambers 15 min after injection. During this phase of the experiment, only the stimulus-appropriate (drug or saline) lever was present; the other lever was removed. Half of the animals were trained to respond on the left lever following drug; the right lever was drug-appropriate for the other half. Responding on the opposite lever was correct following saline. Throughout the shaping procedure the order of drug-saline administration was random, with the restriction that no condition was present for more than three consecutive sessions; sessions were conducted 5–7 days per week.

During the rats' first exposure to the chamber under each condition (drug and saline), the apparatus was programmed for continuous reinforcement (CRF or FR 1) such that each depression of the lever resulted in presentation of water. After stable bar pressing was evident, the schedule of reinforcement was gradually increased until all rats were responding reliably under a fixed ratio 32 (FR 32) schedule following either drug or saline.

Discrimination Training. After responding under the desired ratio (FR 32) was acquired by all animals on each lever, both levers were presented simultaneously. The ratio requirement was maintained on the stimulus-appropriate (correct) lever; there were no programmed consequences for responding on the incorrect lever. The order of drug-saline administration continued as during shaping. All discrimination training sessions were 20 min; accuracy (per cent correct) was defined as the proportion of correct to total responses before the first reinforcer was delivered, i.e., before 32 correct responses occurred.

After all rats reached a criterion of a least 85% correct responding for five consecutive sessions, a fading precedure was introduced. The rats were divided into three groups which were equivalent with respect to accuracy of discrimination. In one group (Group 0.02) the dose of LSD was decreased gradually (from 0.08 mg/kg) in 0.01 mg/kg decrements until the rats were discriminating 0.02 mg/kg from saline. The second group (Group 0.08) was maintained at the original training dose. The third group (Group 0.32) was trained to discriminate a relatively high dose by increasing the LSD dose in 0.04 mg/kg increments until the rats were discriminating 0.32 mg/kg of LSD from saline without severe disruption in response rates.

Testing. After all animals were reliably discriminating the final doses of LSD (0.02, 0.08 or 0.32 mg/kg) at or above criterion, testing was initiated. There were three types of test sessions: (1) dose-response tests, (2) substitution tests and (3) antagonism tests. During any test session, rats were placed into experimental chambers as during training sessions. However, once the rat had emitted 32 responses on either of the two levers, i.e., after successfully completing the required ratio, no reinforcer was delivered, the house lights were turned off, no further responses were recorded and the rat was removed from the chamber. Thus, during test sessions, extinction conditions were in effect. This was done to prevent spurious learning which might bias results when different doses of the same compound were subsequently tested.

During test sessions, data were expressed as the percentage of responses occurring on the drug lever before the ratio was completed on either of the two levers or before 15 min had elapsed, whichever occurred first. Only the data from those rats making at least ten responses were analyzed. Test sessions were conducted no more often than twice per week; at least one LSD and one saline session occurred before each test. Saline sessions always preceded test sessions to minimize possible residual drug effects.

Dose-Response Tests. Rats were injected with various doses of LSD and tested for lever selection in dose-response tests which indicated the relative specificity of the cue to the particular training doses; that is, the amount of LSD needed to produce each cue.

Substitution Tests. Substitution tests were conducted to determine the degree of similarity between a novel compound and different doses of LSD. During these sessions, rats were injected with the novel compound 15–30 min before being placed into the chamber and then tested for lever selection. To test thoroughly for substitution of a drug to the training drug cue, a wide range of doses of each test compound was examined. A drug was said to have substituted only when performance under at least one dose of a test compound did not differ significantly from performance obtained under the training drug.

Antagonism Tests. Rats were injected with either a 5-HT or a DA antagonist 60 min before injection of LSD. Fifteen minutes after LSD, rats were tested in extinction sessions as described above. A drug was said to have had an antagonistic effect whenever there was a significant difference between performance after the drug-antagonist combination and performance after the training drug alone.

Data Analysis. Data from test sessions are presented as the mean percentage of drug-lever responding of all rats successfully completing at least ten responses. Data from each treatment (test drug) were analyzed by means of a two-factor, mixed-effects analysis of variance (ANOVA) with repeated measures (Keppel 1973). In this ANOVA, the two factors were training dose (group) and dose of test drug (dose). The individual main effects of dose and group were analyzed further using Dunn's procedure with $\alpha = 0.05$ as the error rate experimentwise (Keppel 1973) in order to isolate those groups or doses contributing to significant effects. Significant interactions were analyzed further with an analysis of simple main effects (Keppel 1973).

In order to compare each treatment to the preceding LSD or saline performance, a one-way ANOVA with repeated measures (Keppel 1973) was performed which included performance at each dose of the test drug as well as the LSD or saline sessions immediately preceding those test sessions.

Individual means were compared to LSD or saline performance using Dunnett's procedure for comparing all treatment levels to a control with $\alpha = 0.05$ as the error rate experimentwise (Dunnett 1964).

Differences in response rates on LSD and saline sessions for the three groups were analyzed using a two-way ANOVA with repeated measures (Keppel 1973). The slopes of the dose-response curves for LSD were calculated as the ratio of the ED_{84} to ED_{50} (log-probit coordinates) using the method of Litchfield and Wilcoxin (1949).

Drugs. In addition to *d*-lysergic acid diethylamide bitartrate (LSD), the drugs tested in this experiment were: quipazine maleate, MK-212 [6-chloro-2-(1-piperazinyl)-pyrazine] HCl, 5-methoxy-N,N-dimethyltryptamine, 5-methoxytryptamine, *d*-amphetamine sulfate, apomorphine HCl, methiothepin maleate, cyproheptadine HCl, haloperidol (Haldol) and xylamidine tosylate. All doses refer to the above forms. Cyproheptadine was dissolved in 15% aqueous propylene glycol; apomorphine was dissolved in deionized water. Haloperidol was diluted with saline from solutions provided by McNeil Laboratories, Fort Washington, PA, USA. All other compounds were dissolved in isotonic saline (0.9% NaCl). All solutions were injected (IP) in a constant volume of 1 ml/kg.

Results

Acquisition. All 24 rats learned the initial 0.08 mg/kg LSD vs saline discrimination by Session 29. The mean number of sessions to criterion (85% correct) was 20 (range: 8–29). The rats were divided into groups and the fading procedures were initiated on Session 31; thereafter, the group that underwent progressively decreasing doses (Group 0.02) experienced no difficulty in maintaining accurate discriminative performance and the group that underwent progressively increasing doses (Group 0.32) showed little deterioration in response rate. By Session 55, the three groups were discriminating accurately a 16-fold range of LSD doses from saline (0.02–0.32 mg/kg). Throughout the study the percentage LSD responding in all three groups remained between 95–100% on LSD sessions and between 0–5% on saline sessions. Analysis of response rate data for the last 14 discrimination sessions (seven LSD; seven saline) revealed no differences between LSD and saline sessions for any of the groups and no differences between the groups.

Dose-Response Tests. Figure 1 shows the dose-response curves for the three LSD groups. Least-squares analysis revealed that the slope of the dose-response curve for Group 0.02 (4.5) was less steep than those of Group 0.08 (2.0) and Group 0.32 (1.7). The ED_{50} values were 0.002, 0.012, and 0.054 for Groups 0.02, 0.08, and 0.32, respectively.

Substitution Tests. Figure 2 shows the results of substitution tests with the 5-HT agonists quipazine and MK-212. Quipazine produced a dose-related substitution for LSD [$F(3,54) = 4.48$, $P < 0.001$] as well as a significant group effect [$F(2,18) = 3.63$, $P < 0.05$]. The group × dose interaction was not significant. Peak substitutions were 87% in Group 0.02 at 1.0 mg/kg, 83% in Group 0.08 and 88% in Group 0.32, both at 4.0 mg/kg.

The curves for MK-212 are similar to those for quipazine except that MK-212 was about twice as potent. There were

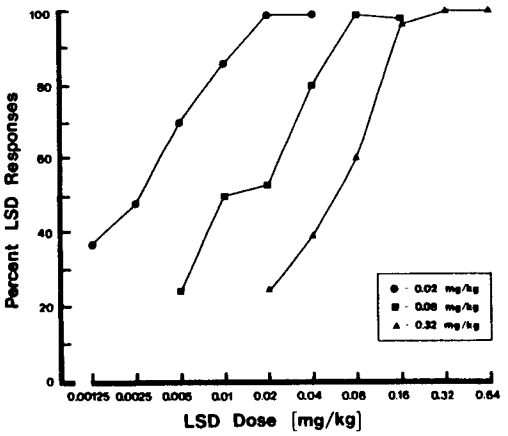


Fig. 1. LSD dose-response relationships for rats trained to discriminate between saline and either 0.02, 0.08 or 0.32 mg/kg of LSD. Each point represents the mean of eight rats

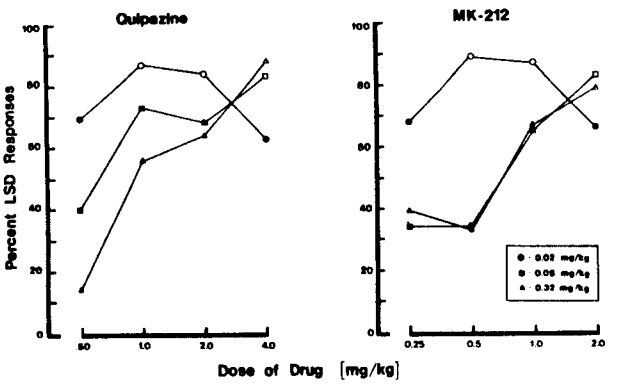


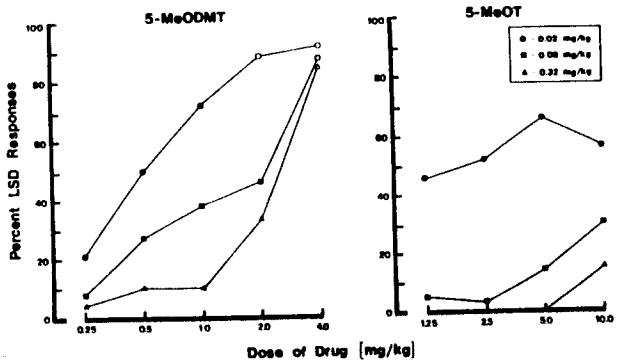
Fig. 2. Results of substitution tests with quipazine and MK-212 in rats trained to discriminate between saline and either 0.02, 0.08 or 0.32 mg/kg of LSD. Each point represents the mean of eight rats. Open symbols represent points that do not differ significantly from LSD performance

significant effects of dose [$F(3,54) = 5.4$, $P < 0.01$], group [$F(2,18) = 3.58$, $P < 0.05$] and group × dose interaction [$F(6,54) = 2.44$, $P < 0.05$]. Analysis of the simple main effects indicated that the largest differences were between Group 0.02 and the other two groups at the 0.25, 0.5 and 1.0 mg/kg doses. Significant substitution occurred in all three groups with the maximum effects being 89% at 0.5 mg/kg in Group 0.02, 83% and 80% at the 2.0 mg/kg dose in Groups 0.08 and 0.32, respectively.

Figure 3 shows the results of substitution tests with two tryptamine derivatives. 5-Methoxy-N,N-dimethyltryptamine (5-MeODMT) produced significant dose [$F(4,72) = 26.1$, $P < 0.001$] and group effects [$F(2,18) = 9.77$, $P < 0.01$]; the interaction was not significant. There were significant differences among all three groups, especially at the lower doses. Significant substitution occurred in all three groups with peak effects of 91%, 87% and 84% at the 4.0 mg/kg dose in Groups 0.02, 0.08 and 0.32, respectively.

5-Methoxytryptamine (5-MeOT) produced little substitution except in Group 0.02. Thus, there were no significant dose or group effects. There was a significant interaction [$F(6,54) = 2.42$, $P < 0.05$] due primarily to the 40–70% LSD-appropriate responses in Group 0.02. No dose of 5-MeOT produced a significant substitution for LSD.

The results of substitution tests with DA agonists *d*-amphetamine and apomorphine are shown in Fig. 4. Neither of these drugs produced any significant effects. Both drugs caused only 10–50% responding on the LSD lever, which was not related either to the dose of test drug or to the LSD training dose. Note that responding following apomorphine was much more consistent across dose than following *d*-amphetamine.



ig. 3. Results of substitution tests with 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) and 5-methoxytryptamine (5-MeOT) in rats trained to discriminate between saline and either 0.02, 0.08 or 0.32 mg/kg of LSD. Each point represents the mean of eight rats. Open symbols represent points that do not differ significantly from LSD performance

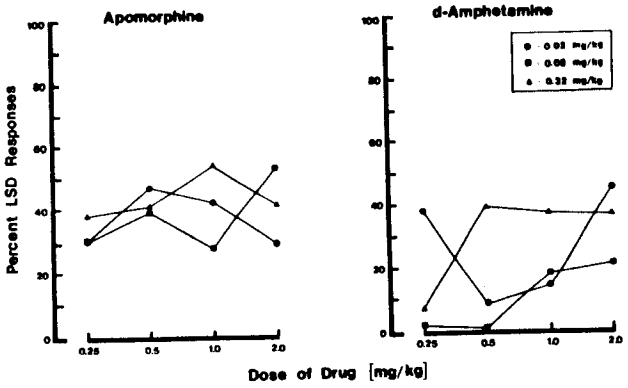


Fig. 4. Results of substitution tests with apomorphine and *d*-amphetamine in rats trained to discriminate between saline and either 0.02, 0.08 or 0.32 mg/kg of LSD. Each point represents the mean of eight rats

Antagonism Tests. The results of antagonism tests are shown in Fig. 5. Methiothepin (MTP) caused a significant dose-related decrease in the percentage of LSD responding [$F(2,30) = 6.88$, $P < 0.005$] when administered 1 h prior to LSD. There were no significant differences between the groups and there was no interaction. Cyproheptadine (CYP) also antagonized all three LSD cues; however, there were no significant effects of dose, group, or the interaction of these variables. Thus, all doses of CYP were equally effective in reducing the discriminability of LSD. Xylamidine tosylate significantly diminished the low dose LSD cue (Group 0.02). Haloperidol had little effect on the LSD cues except for a slight attenuation in Group 0.02. Neither of these compounds produced significant dose, group or interaction effects.

Discussion

As in previous studies using a variety of compounds (Colpaert et al. 1980a; Overton 1979), the present results demonstrate the usefulness of a fading procedure (progressively decreasing doses) as a means of inducing discrimination of very low doses of LSD (0.02 mg/kg). In addition, a new variant of fading, progressively increasing doses, proved successful in enabling rats to discriminate an otherwise behaviorally disruptive dose of LSD (0.32 mg/kg) presumably by inducing behavioral tolerance to each incremented dose. Of particular importance is the fact that, following the incremented dose regimen, the original training dose (0.08 mg/kg) produced only 58% responding on the LSD lever. Thus, the 0.32 mg/kg cue was specific to this higher dose of LSD.

The use of a wide range of LSD training doses (16-fold) allowed a detailed and thorough analysis of the effects of this variable on dose-response, substitution and antagonism tests; quantitative differences among the discriminative properties of LSD in the three groups were often observed. For example, comparison of the slopes of the LSD dose-response curve illustrates that, as the training dose declined, the slope of the LSD gradient became less steep. This relationship has also been

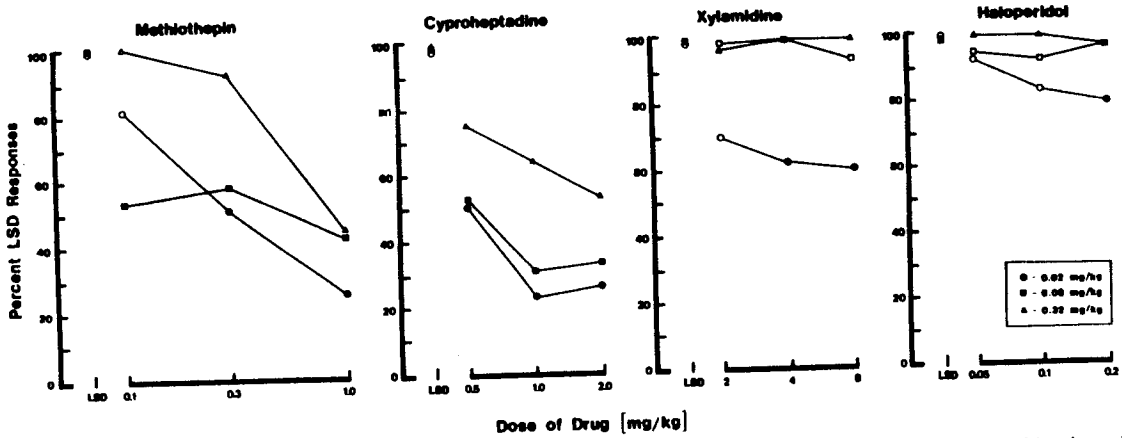


Fig. 5. Results of antagonism tests with methiothepin, cyproheptadine, xylamidine and haloperidol given in combination with LSD in rats trained to discriminate between saline and either 0.02, 0.08 or 0.32 mg/kg of LSD. Each point represents the mean of eight rats. Closed symbols represent performance that is significantly different from LSD alone (represented at the left of each graph)

demonstrated in rats trained to discriminate different doses of fentanyl both with (Colpaert et al. 1980a) and without (Colpaert et al. 1980b) progressively lowering training dose. However, in contrast to the data with fentanyl, the present results cannot be attributed to deterioration of stimulus control since there were no differences among the three groups with respect to accuracy of discrimination.

The results of substitution tests with the direct 5-HT agonists quipazine, MK-212 and 5-MeODMT (Fuller 1980) and antagonism tests with the 5-HT antagonists methiothepin and cyproheptadine (Fuller 1980) reveal significant quantitative differences among the three LSD training dose groups. For example, there were significant differences among the three groups with respect to the doses of quipazine, MK-212 and 5-MeODMT that elicited significant substitution for LSD. Furthermore, as in the LSD dose-response tests, the slopes of the generalization gradients for these agonists were less steep in the low dose LSD group. In fact, the highest doses of quipazine and MK-212 caused decreases in LSD-lever responding; thus, these doses may have exerted actions in addition to those that were similar to the low dose LSD stimulus. Although there were no significant differences among groups during antagonism tests, both methiothepin and cyproheptadine were more effective as antagonists of the low dose LSD stimulus.

The substitutions produced by quipazine and 5-MeODMT also confirm previous reports concerning the similarity (cross-transfer) of quipazine, 5-MeODMT and LSD (Appel et al. 1978; Rosecrans et al. 1978; Rosecrans and Glennon 1979), although recent evidence suggests some differences between the stimulus effects of 5-MeODMT and quipazine (Glennon and Rosecrans 1981). MK-212 which, like quipazine, is a substituted piperazine, was approximately twice as potent as quipazine in eliciting LSD responding, a finding that is in agreement with results from other procedures indicating that MK-212 is a potent stimulant of 5-HT receptors (Clineschmidt and McGuffin 1978). The substitutions of these 5-HT agonists and the antagonism by 5-HT antagonists strengthen the previous conclusion that 5-HT is intricately involved in mediating the discriminative stimulus properties of LSD (Kuhn et al. 1978; Rosecrans et al. 1978; Winter 1978) and, more importantly, extend this conclusion to a wide range of LSD training doses.

Two aspects of these results suggest that, in addition to quantitative differences, qualitative differences among the three LSD groups also existed. In substitution tests with 5-MeOT, a putative endogenous tryptamine (Green et al. 1973) which is rapidly oxidized and which does not readily penetrate the blood-brain barrier (Green et al. 1975), there was a consistent 40 – 70 % substitution in the low dose LSD group across a wide dose range (1.25 – 10.0 mg/kg) whereas there was no such effect in the other two groups. In antagonism tests, the peripheral 5-HT antagonist xylamidine tosylate (Copp et al. 1967) caused a dose-related decrease in per cent LSD responding only in the low dose groups. These two findings suggest that, at this low dose (0.02 mg/kg), the central actions of LSD may be so weak that peripheral actions were also used to form the discrimination.

In contrast to the results obtained with 5-HT agonists, the results of substitution tests with the direct DA agonist apomorphine and the indirect DA agonist *d*-amphetamine (Ernst 1967) revealed no significant effects, i.e., there were no dose-related increases in LSD-lever responding, no significant differences between the three LSD groups and no significant substitutions. Thus, even though the percentage of LSD-lever responding (20 – 55 %) was greater than during saline sessions (0 – 5 %) the fact that this effect was not related either to the dose of these DA agonists or to the training dose of LSD suggests that these results reflect random choice responding (Shannon and Holtzman 1979) rather than partial similarities of LSD and DA agonists. In addition, the results of antagonism tests with the potent DA blocker haloperidol (Janssen 1967) revealed no significant groups or dose effects and no antagonism. Thus, these data indicate that: (1) DA agonists produce a qualitatively different stimulus from that produced by LSD; (2) DA is not intricately involved in the discriminative stimulus properties of LSD; (3) the lack of DA involvement is not related to LSD training dose and (4) comparison across training doses can facilitate interpretation of intermediate results and enhance the value of drug discrimination procedures as an assay of pharmacological action.

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References

Appel JB, White FJ, Kuhn DM (1978) The use of drugs as discriminative stimuli in behavioral pharmacodynamics. In: Colpaert FC, Rosecrans JA (eds) Stimulus properties of drugs: ten years of progress. Elsevier/North Holland Biomedical, Amsterdam, pp 7 – 29

Cameron OG, Appel JB (1973) A behavioral and pharmacological analysis of some discriminable properties of *d*-LSD in rats. Psychopharmacologia 33:117 – 134

Clineschmidt BV, McGuffin JC (1978) Pharmacological differentiation of the central 5-hydroxytryptamine-like actions of MK-212 [6-chloro-2-(1-piperazinyl)-pyrazine], *p*-methoxyamphetamine and fenfluramine in an in vivo model system. Eur J Pharmacol 50:369 – 375

Colpaert FC, Niemegeers CJE, Janssen PAJ (1980a) Factors regulating drug cue sensitivity: limits of discriminability and the role of a progressively decreasing dose in fantanyl-saline discrimination. J Pharmacol Exp Ther 212:474 – 480

Colpaert FC, Niemegeers CJE, Janssen PAJ (1980b) Factors regulating drug cue sensitivity: the effects of training dose in fentanyl-saline discrimination. Neuropharmacology 19:705 – 713

Colpaert FC, Rosecrans JA (1978) Stimulus properties of drugs: ten years of progress. Elsevier/North Holland Biomedical, Amsterdam

Copp FC, Green AF, Randall AW, Sim MF (1967) New peripheral antagonists of 5-hydroxytryptamine. Nature 214:200 – 201

Dunnett CW (1964) New tables for multiple comparisons with a control. Biometrics 20:482 – 491

Ernst AM (1967) Mode of action of apomorphine and dexamphetamine on gnawing compulsion in rats. Psychopharmacologia 10:316 – 323

Fog R (1969) Stereotyped and non-stereotyped behavior in rats induced by various stimulant drugs. Psychopharmacologia 14:299 – 304

Fuller RW (1980) Pharmacology of central serotonin neurons. Ann Rev Pharmacol Toxicol 20:111 – 127

Glennon RA, Rosecrans JA (1981) Speculations on the mechanism of action of hallucinogenic indolealkylamines. Neurosci Biobehav Rev 5:197–207

Green AR, Hughes JP, Tordoff AFC (1975) The concentration of 5-methoxytryptamine in rat brain and its effects on behavior following its peripheral injection. Neuropharmacology 14:601–606

Green AR, Koslow SH, Costa E (1973) Identification and quantification of a new indolealkylamine in rat hypothalamus. Brain Res 51:371–374

Hirschhorn ID, Rosecrans JA (1974) A comparison of the stimulus effects of morphine and lysergic acid diethylamide (LSD). Pharmacol Biochem Behav 2:361–366

Jarbe TUC, Rollenhagen C (1978) Morphine as a discriminative cue in gerbils: drug generalization and antagonism. Psychopharmacology 58:271–275

Janssen PAJ (1967) The pharmacology of haloperidol. Int J Neuropsychiat 3:10–18

Kelley PH, Iversen LL (1975) LSD as an agonist at mesolimbic dopamine receptors. Psychopharmacologia 45:221–224

Keppel G (1973) Design and analysis: a researcher's handbook. Prentice-Hall, Englewood Cliffs

Kuhn DM, White FJ, Appel JB (1978) The discriminative stimulus properties of LSD: mechanism of action. Neuropharmacology 17:257–263

Litchfield JT, Wilcoxin F (1949) A simplified method for evaluating dose-effect experiments. J Pharmacol Exp Ther 96:99–113

Overton DA (1979) Drug discrimination training with progressively lowered doses. Science 205:720–721

Pieri L, Pieri M, Haefely W (1974) LSD as an agonist of dopamine receptors in the striatum. Nature 252:586–588

Rosecrans JA, Glennon RA (1979) Drug-induced cues in studying mechanisms of drug action. Neuropharmacology 18:981–989

Rosecrans JA, Krynock GM, Newlon PG, Chance WT, Kallman MJ (1978) Central mechanisms of drugs as discriminative stimuli: involvement of serotonin pathways. In: Colpaert FC, Rosecrans JA (eds) Stimulus properties of drugs: ten years of progress. Elsevier/North Holland Biomedical, Amsterdam, pp 83–98

Shannon HE, Holtzman SG (1979) Morphine training dose: a determinant of stimulus generalization to narcotic antagonists in the rat. Psychopharmacology 61:239–244

Teal JJ, Holtzman SG (1980) Discriminative stimulus effects of cyclazocine in the rat. J Pharmacol Exp Ther 212:368–376

White FJ, Simmons MA, West KB, Holohean AM, Appel JB (1980) The effect of serotonin depletion on the discriminability of LSD. Pharmacol Biochem Behav 13:569–574

Winter JC (1978) Stimulus properties of phenylethylamine hallucinogens and lysergic acid diethylamide: the role of 5-hydroxytryptamine. J Pharmacol Exp Ther 204:416–423

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