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Discriminative Stimulus Properties of Lysergic Acid Diethylamide in the Monkey

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ABSTRACT

Four monkeys (*Cercopithecus aethiops*) were trained to discriminate 0.06 mg/kg of lysergic acid diethylamide (LSD) from saline in a two-key task in which correct responding was reinforced with food under a fixed ratio 32 schedule. The ED_{50} of LSD was 0.011 mg/kg. The nonhallucinogenic ergot, lisuride, and the hallucinogen, 5-methoxy-N,N-dimethyltryptamine, substituted completely for LSD (ED_{50} values were 0.0098 and 0.45 mg/kg, respectively). Mescaline (1–40 mg/kg), *d*-amphetamine (0.1–0.625 mg/kg) and apomorphine (0.1–0.5 mg/kg) did not substitute for LSD. In antagonism testing with ketanserin (1–10 mg/kg) or pirenperone (0.025 and 0.05 mg/kg), only the highest dose of pirenperone attenuated the LSD stimulus effect (to 55%). A 0.1-mg/kg dose of pirenperone produced nonresponding in three of four animals. The LSD cue was unaffected by clozapine (1 and 2 mg/kg), haloperidol (0.1 mg/kg) and pizotifen (0.6–1.8 mg/kg). The fact that lisuride does not readily cause hallucinations in humans, but yet substituted for LSD in primates, indicates that the LSD cue may not reflect the hallucinogenic properties of LSD. It is suggested that the LSD stimulus effect may depend on receptors (*e.g.*, serotonergic) that, at the moment, are only poorly characterized.

Drug cues in animals have been said to model human verbal reports (White and Appel, 1982a) and, for this reason, DD has been used to assess euphoria, pain and similar subjective (private, internal) events (Lal, 1977; Weismann, 1976). For example, much interest has been expressed in drug cues elicited by hallucinogens, an interest that is particularly important because a reliable animal model for hallucinosis does not exist elsewhere (Stoff *et al.*, 1978; Marini and Sheard, 1981). Hallucinogens are powerful inducers of stimulus control in DD. In rats, for example, the lowest reported discriminable dose of LSD is 5 μg/kg (Greenberg *et al.*, 1975). Furthermore, hallucinogen cues are generally interchangeable (*i.e.*, the drugs readily substitute for each other; Appel *et al.*, 1978; Glennon and Rosecrans, 1982).

However, some nonhallucinogenic drugs have been reported to mimic hallucinogens in DD situations. Thus, in animals trained to discriminate LSD from saline, the nonhallucinogenic ergot, lisuride, substitutes for LSD and *vice versa* (White and Appel, 1982a). In addition, these drugs are similar in several other ways; notably, both reduce 5-HT cell firing in dorsal raphé nuclei (Rogawski and Aghajanian, 1979) and inhibit [^{3}H]5-HT, [^{3}H]LSD and [^{3}H]spiroperidol binding to DA and 5-HT receptors (Fillion *et al.*, 1978; Peroutka and Snyder, 1979; Hruska and Silbergeld, 1981; Rosenfeld and Makman, 1981). However, doses of up to 2 mg/day of lisuride fail to induce hallucinations in humans consistently (De Cecco *et al.*, 1979; Chiodini *et al.*, 1981). In contrast, threshold LSD doses of 0.025 to 0.05 mg induce hallucinations readily (Freedman and Boggan, 1981). Lisuride is a clinically important drug which is used for treating a variety of diseases primarily involving DA dysfunction, *e.g.*, parkinsonism, hyperprolactenemia and acromegaly (Calne *et al.*, 1983). Lisuride is also used in migraine prophylaxis, which may involve a 5-HT-mediated effect (Calne *et al.*, 1983; Podvalová and Dlabač, 1972).

DD analysis has aided in the detection of the neuropharmacological differences between lisuride and LSD (White and Appel, 1982a). Thus, it was shown that the lisuride cue is mediated primarily by DA whereas the LSD cue involves 5-HT (see also White and Appel, 1982b; Kuhn *et al.*, 1978). Given that both lisuride and LSD affect DA and 5-HT in other situations (above), their differential cue substrate may be taken to indicate that each compound has both DA and 5-HT properties in DD situations. However, the action at one neurotransmitter site may overshadow the other during acquisition of the respective cues. That the drugs substitute for each other may suggest further that each compound exerts sufficient action at the less cue-prevalent system (*i.e.*, 5-HT or DA) to promote

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ABBREVIATIONS: DD, drug discrimination; LSD, lysergic acid diethylamide; 5-HT, 5-hydroxytryptamine; DA, dopamine; 5-MeODMT, 5-methoxy-N,N-dimethyltryptamine.

interchangeability of the drugs in the DD situation. Nevertheless, the findings with lisuride and LSD still pose a challenge with respect to the basis for the cueing effect of LSD if it does not involve the hallucinogenic properties of the drug.

This study investigated the possible role of species differences in LSD discrimination by examining the pharmacology of the LSD cue in the monkey (*Cercopithecus aethiops*). Because the effects of drugs sometimes show well-characterized relationships with control rates of responding (Thompson *et al.*, 1981), and because such rate-dependency has been said to reflect the impact of changes in the stimulus context, externally or internally (*e.g.*, drug-induced), upon behavior (McKim, 1981) the effects of LSD upon the rate of responding were also examined.

Methods

Animals. Four male, adult, African queen vervet monkeys (*Cercopithecus aethiops*) were used. The animals (no. 49, 50, 51 and 52) weighed 5.5, 6.9, 4.9 and 6.3 kg, respectively, at the beginning of the experiment. Three animals were approximately of the same age (4–6 years), whereas one animal (no. 50) was at least one year older; it had been used unsuccessfully for breeding. All animals were born in the wild of West Africa and were drug naive, except for routine Ketalar (Parke-Davis & Co., Soeborg, Denmark) anesthesia, which had been used 2 to 5 times during an initial 8 weeks of quarantine and health examinations at the Danish Serum Institute (Copenhagen, Denmark). The animals were transferred to our laboratory where they were housed individually in wire-mesh squeeze cages (60 × 100 × 60 cm), which were placed in a room of constant 23 ± 1°C temperature. After 16 weeks of habituation to the laboratory, the animals were deprived to a constant 88.5 to 92.5% level of their free-feeding weights by restricting food intake. Thus, the monkeys received (in experimental sessions; below) a daily maximum of 30 1-g banana reward tablets (no. 004C0; Bioserv, Inc., Frenchtown, NJ), which were supplemented with 10 to 110 g of standard laboratory monkey chow plus fresh fruit as well as vitamin drops. Water was always freely available. The animals were weighted twice weekly.

Apparatus. An operant panel was used; it was built inhouse and accommodated two translucent primate response keys (type PPC-002; BRS/LVE, Beltsville, MD), located to the right and left of a food receptacle which was connected to an automated pellet feeder (type PDC-005, BRS/LVE) placed behind the panel. The response keys, mounted in separate slots, were indented backwards at a 45° angle from upright position. The panel could be installed in the front wall of the homecage of the animal by lifting a slide door. This would place the response keys within eye-sight of the animal when it was sitting in the bottom of its cage.

A window air-conditioner fan provided constant masking noise during experimental sessions (below) which were conducted in the homecage in the colony room. Closed-circuit TV was used to monitor the behavior of the animal. An ALPHA-LSI 16 computer (Computer Automation, Inc., Irvine, CA), located in an adjacent room, was programmed to control experimental events and to collect response data (below).

Shaping procedure. The animals were initially required to press a response key to obtain a pellet according to a continuous reinforcement schedule. No shaping was necessary; simply allowing the animals access to the panel resulted in the spontaneous occurrence of key-pressing behavior. The session started when one of the response keys was transilluminated (left key, green light; right key, red light); the key-color assignments remained constant throughout the experiment. Different lights were used to facilitate the discrimination of the position of the keys because reinforcement on one or the other key was made dependent upon the prior injection (below) of LSD or saline (vehicle control), respectively. Thus, after LSD, only responding on a designated (drug) key was reinforced. Responding on the opposite key never had any programmed consequences. However, after saline injections, only responding on the key opposite to the drug key was reinforced. The assignment of drug and saline keys was identical for animals no. 49 and 50, but was symmetrically reversed for no. 51 and 52. This was done in order to distribute any left/right handedness. Daily sessions were conducted in an irregular order with respect to LSD-saline pretreatments. However, each treatment did not occur for more than three consecutive sessions.

During this initial phase of the training, only the injection-appropriate stimulus key was illuminated. The schedule of reinforcement was gradually increased from continuous reinforcement to fixed ratio 32 (the final schedule). Sessions lasted 20 min, or when a maximum of 30 reinforcers had been obtained. Animal no. 50, however, was allowed a session time of 27 min due to its unusually slow rate of responding. Supplementary rations of food (above) were always given at least 1 hr after experimental sessions. These were conducted 5 to 7 days/week.

Discrimination training. Once the animals were responding reliably under the fixed ratio 32 schedule during both saline and LSD sessions both keys were illuminated simultaneously during sessions. The initial dose of LSD was 0.02 mg/kg. Subsequent adjustments were made such that the final dose eventually reached was 0.06 mg/kg. During further discrimination training sessions, the animals eventually learned to choose the correct response key according to the injection of LSD or saline. Care was taken to clean the keys after the session of each animal in order not to provide possible cues other than those related to the injection, as to which key was reinforced.

The following data were recorded from each session: total number of responses on the correct and incorrect keys, number of reinforcements, time to obtain the first reinforcement (reaction time), number of correct and incorrect responses before the first reinforcement and session time. Discrimination accuracy was expressed as the percentage of responses on the correct key before the first reinforcement.

A criterion of discrimination accuracy, group mean > 90% during five LSD and five saline training sessions, was set to ensure stable discrimination performance before drug testing (below) was instituted.

Drug testing. Test sessions were conducted every 2 to 4 days provided that the animals attained a group criterion of >90% discrimination accuracy (>75% for individual animals). In substitution testing, novel drugs, or other doses of LSD, were administered in order to assess the similarity to the LSD cuing effect. In antagonism testing, drugs were administered in conjunction with LSD in order to determine degree of attenuation of the LSD stimulus effect. A test session was terminated without reinforcement when the animal had emitted 32 responses on either key or when the maximum session time had elapsed. The animals later received an added ration of supplementary food.

Only discrimination data from sessions in which at least two animals responded with more than 10 responses each were included in statistical analyses (below).

Drugs. The following drugs were dissolved in distilled water and injected in a volume of 0.1 ml/kg, except when noted otherwise. Injections were s.c. in the lower back region and the injection-test intervals (*t*-min) were: *d*-amphetamine sulfate (Sigma Chemical Co., St. Louis, MO), *t*-30 min; apomorphine HCl (Sigma), *t*-15 min; clozapine (Sandoz, Basel, Switzerland) dissolved in a minimum amount of 0.2 N HCl and brought up to volume with water, *t*-45 min; haloperidol (Janssen Pharmaceutica, Beerse, Belgium) diluted from ampules (Haldol; 5 mg/ml) with water, *t*-120 min; ketanserin bitartrate (Janssen) injected in a fixed concentration of 10 mg/ml distributed at 2 to 3 s.c. sites, *t*-60 min; lisuride hydrogen maleate (Schering AG, Berlin, BRD), *t*-30 min; *d*-LSD bitartrate (National Institute on Drug Abuse, Research Triangle Park, NC or Sandoz) dissolved in saline and stored in ampules at −18°C for no longer than 6 weeks, *t*-30 min (except as indicated, below); mescaline HCl (Sigma) injected in volumes of 0.5 to 2 ml/kg distributed at 2 to 3 s.c. sites, *t*-30 min; 5-MeODMT (Sigma) injected in volumes of 0.1 to 0.4 ml/kg, *t*-30 min; pirenperone (Janssen) dissolved in a minimum amount of 0.2 N HCl and brought up to volume with water, *t*-30 min; and pizotifen maleate (Sandoz) injected in vol-

umes of 0.1 to 0.6 ml/kg, t-60 min. Saline (0.9%) was given as vehicle control (0.1 ml/kg).

Statistical analysis. The stability of base-line discrimination accuracy (expressed as the percentage of responses on the LSD-key), reaction time and overall response rate (total number of responses in the session/session time), comprising data from individual LSD and saline training sessions immediately preceding test sessions, were analyzed by analysis of variance for a repeated measures design using the GLM programme (SAS Institute, Inc., Cary, NC). Inasmuch as this analysis indicated that changes in base-line levels did not occur over time (below), these data were pooled across sessions for individual animals to provide single average base-line levels for evaluating drug effects. However, because the training dose of LSD (0.06 mg/kg) both increased and decreased response rate, depending on the control rate of the individual animals, the analysis of the effect of LSD on response rate was made on the absolute percentage of deviation from the saline control rate in individual animals. The relationship between the effect of LSD and the control rate of responding was analyzed further by linear regression analysis (Snedecor and Cochran, 1967) combined with analysis of variance and Student's t test (*ibid*) for assessing the significance of the regression parameters.

The effect of the drug treatments upon discrimination accuracy and reaction time was analyzed by analysis of variance (above). Dose effects were analyzed with the PROBIT programme (SAS Institute, Inc.) which generated ED_{50} values based on log-probit relationships.

Acquisition sessions in which an animal was less than 50% accurate in key-choice were designated error sessions. Their numbers were accumulated for individual animals, and a χ^2 test was used to evaluate differences between animals.

Results

Stimulus control by LSD was evident from the very beginning of discrimination training (fig. 1). However, LSD did not appear to produce stable stimulus control until the dose was increased to 0.06 mg/kg. Asymptotic discrimination performance eventually stabilized around 90 to 95% accuracy. The number of error sessions during acquisition were 9 (no. 49), 7 (no. 50), 19 (no. 51) and 7 (no. 52). The χ^2 test showed that these numbers were significantly different from 10.5, the average for the group (χ^2 = 9.43, dF = 3, P < .05). Thus, significant differences existed between animals with respect to acquiring the discrimination. Test sessions were initiated after the 67th training session. The average levels of accuracy during the last five LSD and five saline training sessions were 91.7 and 92.3%, respectively.

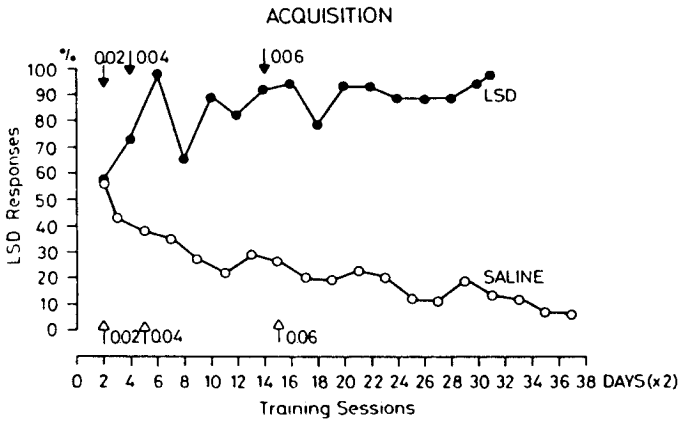

Fig. 1. Acquisition of the LSD-saline discrimination. The data points represent the average percentage of responses on the LSD key in a group of four monkeys after LSD or saline injections 30 min before training sessions. ↑, indicates interval points for adjustment of the LSD dose (initial dose = 0.02 mg/kg) in LSD training sessions. ⇧, indicates interval points for adjustment of the LSD dose in LSD training sessions in between the corresponding saline training sessions. The data are from individual sessions, or blocks of two sessions.

Table 1 summarizes the individual performance of the animals expressed as an average of base-line sessions, pooled across the entire experiment as values did not change significantly over time. These pooled base-line levels represent the controls against which drug effects were evaluated. In addition to the discriminative effect produced by LSD, the drug also affected response rate when compared to saline (control) levels (table 1). Thus, when expressing response-rates under LSD (for individual animals) as an absolute percentage of deviation from the saline (control) levels (see Statistical analysis under "Methods") there was a significant main effect of LSD upon response rate change (F (1,6) = 12.77, P < .05). There was no main effect upon reaction time (F (1,6) = 0.71, N.S.). However, there was a significant animal × drug (LSD) interaction for the response rate effect: F (6,328) = 14.21, P < .0001. This latter result reflects the fact that the effect of LSD upon the rate of responding was dependent upon the base-line levels in individual animals. Figure 2 depicts this relationship graphically. Here, the log (LSD effect) is plotted against the log (control rate) following conventional rate-dependency metrics (Dews and Wenger, 1977). A regression line, fitted through the points from individual animals, was highly significant [F (1,2) for regression was 59.73, P < .025; t for the slope ≠ 0 was 7.73, dF = 3, P < .005).

Figure 3 shows the time course of the LSD cue. After injection of the training dose of LSD (0.06 mg/kg), the onset of the cue was exceedingly rapid, the time to half-maximal effect being approximately 3.8 min. The effective duration of the cue was at least 60 min.

The results of substitution tests are shown in figure 4. The slope of the dose-response curve for LSD was relatively shallow as the ED_{50} (0.011 mg/kg) was 18% of the training dose. A complete substitution for LSD was produced by lisuride at a dose of 0.03 mg/kg. Although a higher lisuride dose (0.06 mg/kg) produced less than maximal LSD-like effect, this dose also increased reaction time significantly. The ED_{50} of lisuride was 0.0098 mg/kg. 5-MeODMT substituted completely for LSD (ED_{50} = 0.45 mg/kg) and no dose of 5-MeODMT affected reaction time. Mescaline did not substitute for LSD although the percentage of LSD responses was nonsignificantly increased above the saline level after the highest dose of mescaline (40 mg/kg). This dose did, however, significantly increase reaction time. Finally, both amphetamine and apomorphine failed to substitute for LSD. Only the highest dose of apomorphine (0.5 mg/kg) increased reaction time significantly.

Ketanserin and pirenperone produced only a small and nonsignificant block of the LSD cue (fig. 5). The partial antagonistic effect of pirenperone occurred in doses that significantly affected reaction time. For example, after 0.05 mg/kg of pirenperone only two animals completed the test and nonresponding occurred in 3 of 4 animals after 0.1 mg/kg. The 10-mg/kg dose of ketanserin produced ataxia and salivation whereas the two highest doses of pirenperone (0.05 and 0.1 mg/kg) induced a stupor-like syndrome in which the animals showed prolonged staring at the back wall of their cages. The back-wall staring behavior has been noted previously in our laboratory only after spiroperidol (unpublished observations).

Finally, pizotifen (0.6–1.8 mg/kg), clozapine (1 and 2 mg/kg) and haloperidol (0.1 mg/kg) failed to alter the stimulus effect

TABLE 1

Base-line LSD discrimination performance

Base-line performance levels for individual animals pretreated with the training dose (0.06 mg/kg) of LSD or saline (control). Reaction time is the time to complete the first 32 responses (= 1 fixed ratio). Response rate is calculated as the total number responses in the session divided by the session time. The data represent the average levels (±S.E.M.) of 40 LSD and 44 saline training sessions, respectively, which preceded test sessions.

Monkey No.	Discrimination Accuracy		Reaction Time		Response Rate	
	Saline	LSD	Saline	LSD	Saline	LSD
	% LSD responses		*sec*		*responses/min*	
49	6 ± 1	100 ± 0	12 ± 1	9 ± 2	94 ± 3	99 ± 6
50	0 ± 0	99 ± 0	43 ± 5	228 ± 51	51 ± 2	18 ± 2
51	0 ± 0	98 ± 1	6 ± 0	12 ± 1	73 ± 4	59 ± 4
52	2 ± 0	100 ± 0	12 ± 1	8 ± 1	99 ± 6	145 ± 4

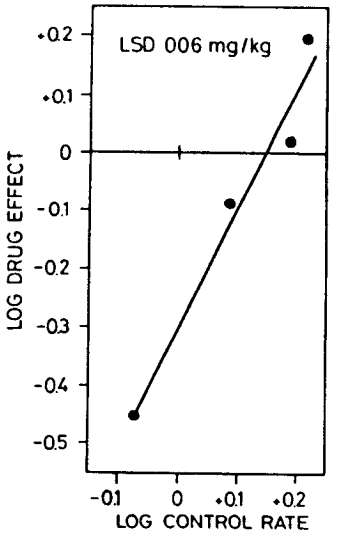

Fig. 2. Rate-dependency of the effect of LSD on response rate. The effect of the training dose of LSD (0.06 mg/kg) is expressed as log (LSD response rate divided by saline response rate) using the data from table 1 (response rates converted to responses/second). The equation for the regression line, $y = 1.99\ x - 0.3$, indicates a strongly rate-dependent LSD effect: low control rates are decreased by the drug whereas high control rates are increased.

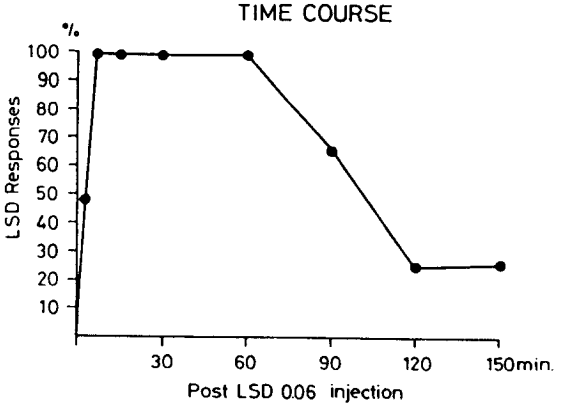

Fig. 3. Time course of the LSD cue. The data points represent the average percentage of LSD responses in a group of four monkeys trained to discriminate 0.06 mg/kg of LSD (injected 30 min before training) from saline. Injections of this dose of LSD were given at various times, as indicated, before test sessions.

of LSD, although only the highest dose of clozapine (2 mg/kg) significantly increased reaction time. Haloperidol in a dose of 0.3 mg/kg produced dystonia such that no responding occurred.

Discussion

The discriminability of LSD has been reported previously in rats (Hirschhorn and Winter, 1971; Cameron and Appel, 1973) and pigeons (Järbe, 1980). The present results confirm the finding that LSD has discriminable stimulus properties and extends this observation to the monkey. As in other species, the time course of the LSD cue in the monkey appears to be relatively short (1–2 hr). This has previously (Cameron and Appel, 1973; Järbe, 1980) been taken to indicate the similarly short-lasting presence of the drug in brain tissue after systemic administration. In comparison, the human plasma LSD levels correlate with the experienced effects of the drug (half-life time approximately 4 hr; Freedman and Boggan, 1981). Thus, the animal DD situation may correspond best to the (acute) direct effects of LSD in humans, although such a comparison is difficult to make given that drug sensitivity in the DD situation is largely dependent upon the training dose (White and Appel, 1982c).

In addition to the ability of LSD to elicit a cueing effect, the drug also affected the rate of responding. However, the finding that this latter effect was dependent upon the base-line (saline) rate of responding is contrasted by the lack of such clear effect when the drug is given acutely (Thompson *et al.*, 1981). In this situation, response-pausing, possibly confounding rate-dependency, often occurs (Rech and Commissaris, 1982). However, the development of tolerance to the pausing effect when the drug is given chronically (Freedman *et al.*, 1964), may unmask rate-dependent drug effects. Thus, the formation and maintenance of stimulus control by LSD was paralleled by "rate-dependent" response-rate changes and neither effect showed tolerance over time.

The similarity of LSD discrimination parameters across species suggests that the DD procedure can detect an important, possibly direct, pharmacological effect of the drug. However, because in the present experiment lisuride substituted for LSD, the LSD stimulus effect may not reflect, *per se*, the hallucinogenic properties of LSD. If correct, it would seem to imply that it should be possible to demonstrate nonhallucinogenic discriminable effects of LSD. That this may be so is indicated by the recent observations that LSD was found to substitute 1) for lisuride (White and Appel, 1982a); 2) for ergonovine and lergotrile (Cunningham *et al.*, 1983), two clinically used ergots which do not cause hallucinations in therapeutic doses (Goldstein *et al.*, 1980); 3) for the precursor of 5-HT, *l*-5-hydroxytryptophan (Callahan *et al.*, 1983) which is used clinically for its hypnotic effect (Hartman *et al.*, 1975); 4) partially for fenfluramine, a serotonergic anorectic compound (White and

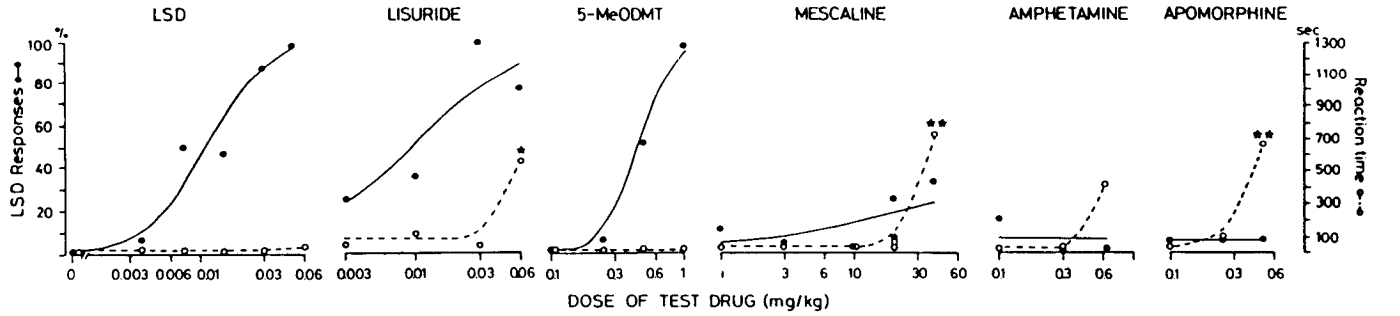

Fig. 4. Substitution testing. The test drugs were given (alone) to monkeys trained to discriminate the stimulus properties of 0.06 mg/kg of LSD from saline. Also shown is the dose-response of LSD; the 0 and 0.06 mg/kg of LSD points represent base-line (training) performance. All curves are fitted on the basis of probit analysis. The solid lines indicate the LSD cue similarity whereas dotted lines represent reaction time (*i.e.*, average time to complete 32 responses on either response key).

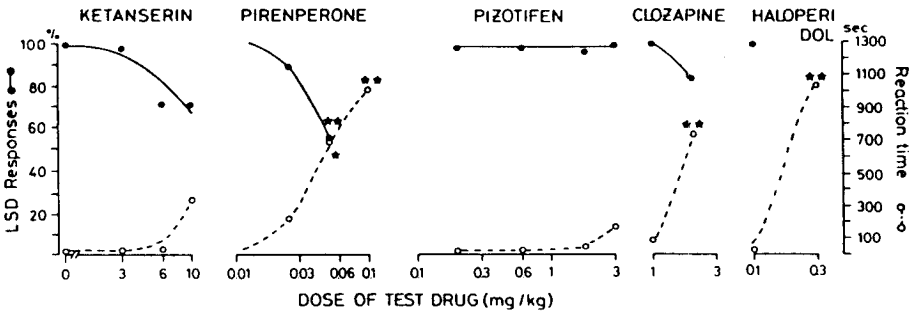

Fig. 5. Antagonism testing. The test drugs were given in conjunction with 0.06 mg/kg of LSD (the training dose). The base-line performance after LSD alone is shown at 0 mg/kg ketanserin. Discrimination performance could not be obtained reliably (data not shown) after some drug treatments (*e.g.*, pirenperone, 0.1 mg/kg) due to behavioral disruption. See legend to figure 4 for other details.

Appel, 1981); and 5) partially for apomorphine, a DA agonist which causes emesis in humans (Holohean *et al.*, 1982).

That LSD substitutes partially or completely for several nonhallucinogens indicates that the discriminable effects of LSD (and, possibly, of other drugs) are dependent upon the discrimination (training drug) history of the animal; *i.e.*, the particular pharmacological action that the animals are trained to "attend" to (see also Appel *et al.*, 1982; Glennon and Young, 1984). Furthermore, the likelihood that LSD exerts nonhallucinogenic discriminable effects indicates that at least one of those could be the basis for the drug's own cueing properties.

The finding that the direct 5-HT agonist, 5-MeODMT, substituted for LSD is in agreement with similar results obtained in rats (White and Appel, 1982c; Young *et al.*, 1982). The pharmacological specificity of this interaction was indicated by the inability of the DA agonist, apomorphine, and of amphetamine to substitute for LSD, again paralleling data obtained in rats (*ibid*). Furthermore, both the DA antagonist, haloperidol, and clozapine which blocks both DA and *alpha*-1 adrenergic receptors (Browne and Koe, 1982), failed to affect the LSD cue. Taken together, these observations are not inconsistent with the long-standing notion that the LSD cue is mediated primarily by activation of some (postsynaptic) 5-HT receptors (Kuhn *et al.*, 1978; Colpaert *et al.*, 1982; White and Appel, 1982a,c). It is tempting to speculate that the corresponding presynaptic neurons may reside in the dorsal raphé as electrophysiologically identified 5-HT cells in this area are inactivated by very low doses of both lisuride and LSD (Rogawski and Aghajanian, 1979) and no tolerance to the effect of LSD develops (*ibid*). Furthermore, in animals trained to discriminate electrical stimulation of this area from no stimulation, LSD mimics the effect of the stimulation (Hirschhorn *et al.*, 1975).

The demonstration of 5-HT receptor heterogeneity (Peroutka and Snyder, 1979; Gozlan *et al.*, 1983; Nelson *et al.*, 1983), and the availability of drugs (*e.g.*, ketanserin, pirenperone and pizotifen), which are selective toward at least one receptor subtype (*e.g.*, 5-HT_2; Leysen *et al.*, 1982; Colpaert and Leysen, 1981), suggest a basis for further clarification of the 5-HT involvement in the cuing effect of LSD. Thus, it was reported that the stimulus effects of 0.08 and of 0.16 mg/kg of LSD were blocked by both pirenperone, ketanserin and pizotifen (Colpaert *et al.*, 1982; Nielsen *et al.*, in press). Furthermore, pirenperone and ketanserin also block the cue elicited by the 5-HT agonist 1-(2.5-dimethoxy-4-methylphenyl)-2-aminopropane, an agent which is substituted for by LSD, mescaline, 5-MeODMT and quipazine (Glennon *et al.*, 1983). Thus it would appear that antagonism of the LSD cue requires blockade of 5-HT_2 receptors.

The present data, however, question that 5-HT_2 receptor antagonism is sufficient for blockade of the LSD cue under all circumstances (LSD-training dose, species, etc.) because the selective 5-HT_2 antagonists pirenperone and ketanserin at best attenuated the stimulus effect of LSD. In addition, pizotifen and clozapine, which both block 5-HT_2 receptors (Leysen *et al.*, 1982), also failed to affect the LSD cue. Furthermore, the present inability of mescaline to substitute for LSD supports the noninvolvement of these receptors in the LSD-cue as mescaline has been used to model 5-HT_2 receptor activation pharmacologically (Niemegeers *et al.*, 1983). Finally, it should also be noted that although pirenperone, for example, blocks the LSD cues in rats (Colpaert and Janssen, 1983), this occurs in a fashion which indicates a more complex interaction than a simple agonist/antagonist interaction (*ibid*).

On the converse, the involvement of at least some 5-HT receptors in the present LSD cue was indicated by the finding of complete substitutions for LSD by the 5-HT agonists, lisuride and 5-MeODMT. When comparing these data to results from receptor binding studies, it can be noted that LSD (and

lisuride) binds to 5-HT_2 receptors as well as to 5-HT_1 sites (which may comprise multiple subtypes; Peroutka and Snyder, 1979; Nelson *et al.*, 1983). Inasmuch as the antagonists in the present study are selective toward 5-HT_2 receptors and because at least 5-MeODMT has higher affinity for 5-HT_1 sites than for 5-HT_2 receptors (Martin and Sanders-Bush, 1982), it would appear to indicate a preferential role for 5-HT_1 sites in mediating the LSD stimulus effect. However, the further investigation of this hypothesis awaits the clarification of the issue of 5-HT receptor subtypes as well as the development of drugs which are selective for these putative subtypes.

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