LSD-25 as a Discriminative Stimulus for Response Selection by Pigeons

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JÄRBE, T. U. C. *LSD-25 as a discriminative stimulus for response selection by pigeons.* PHARMAC. BIOCHEM. BEHAV. 13(4) 549–554, 1980.—Pigeons (N=4) were trained to discriminate between the effects induced by intramuscular (IM) injections of d-LSD and saline using a discrete-trial discrimination paradigm (choice between left and right hand key) in a conventional operant box. The solutions were administered IM 15 min prior to the sessions. A FR 15 schedule was in operation to produce food. Which of the two keys was correct on a given training session depended upon whether LSD or saline had been given. Three of the birds were trained and maintained with a dose of 40 μg/kg of LSD and the fourth pigeon finally was maintained on 50 μg/kg of LSD. The dose resulting in 50% LSD appropriate responding (ED$_{50}$) was 18 μg/kg and the median time-interval for the decay of the LSD stimulus (40 μg/kg) was 84 min. Tests with psilocybin (ED$_{50}$=0.55 mg/kg) and N,N-dimethyltryptamine (ED$_{50}$=5.7 mg/kg) resulted in responding appropriate for the LSD training condition. Mescaline injections above 10 mg/kg severely suppressed responding. The frew responses emitted after tests with 15 and 20 mg/kg of mescaline were directed to the LSD associated key. Tests with BOL (0.1 to 3 mg/kg) as well as three other psychotropic drugs (Δ^9-tetrahydrocannabinol, morphine and, pentobarbital) did not result in responding above 50% LSD appropriate responses. As a possible antidote, methergoline, a putitative antagonist of post-synaptic serotonin receptor sites, was administered 75 min prior to testing the cueing properties of LSD. No definitive role for a blocking effect of the LSD-cue is provided by the present data.

LSD discrimination   Pigeons   Psychedelics   Non-psychedelics   Methergoline

D-LYSERGIC acid diethylamide (LSD) and related psychedelics induce marked, characteristic changes in perception and mood in man. People report alterations in most modalities [10]. Even though these events may be unique to man, animal models have been used to study the neurochemical/pharmacological basis for the action of psychedelics like LSD, psilocybin and mescaline. Among the known putative transmitters, 5-hydroxytryptamine (5-HT) mostly have been implicated in the mechanism of action of psychedelic drugs [1, 2, 5, 7] although binding to dopamine receptors also has been described [11, 32, 40]. It is even possible that there exist a specific binding site for LSD in the rat brain [29].

Most behavioral methods used to study psychedelic compounds have relied on measurements of rates of ongoing behaviors but similar behavioral effects may be produced with different kinds of drugs. The drug discrimination paradigm, on the other hand, is both specific and sensitive [3,4]. In this situation drugs are studied with reference to their ability to serve as discriminative stimuli, thereby guiding the choice behavior of animals. Within this framework, LSD, mescaline and psilocybin have been shown to control differential responding in rats [8, 25, 43]. The interoceptive cues generated by the drugs appear to be similar since drug-psychedelic appropriate responding is maintained when these drugs are substituted for one another. Other psychotropic compounds (e.g., amphetamine, cocaine, barbital and morphine) do not generalize to the psychedelics when tested by substitution in rats trained to discriminate between the effects of a psychedelic agent and the saline condition [25].

Because of the peculiar effects induced by psychedelics it seemed of interest to determine if such compounds possess similar stimulus characteristics also in a non-mammalian species. Pigeons were trained to discriminate between LSD and saline and the animals were then tested with other psychedelics and nonpsychedelic drugs as well as methergoline, a purported 5-HT antagonist.

METHOD

Animals

The subjects were 4 experimentally naive, mature male pigeons of a mixed strain (Estuna AB, Sweden). The free-feeding weights of the birds ranged between 310 ± 354 g, averaging 338 g. Between the experimental sessions the birds were individually housed in a larger colony room (light from 8.00–20.00 hr; temp. 20°–22°C; relative humidity 50%–55%). During the experiments the birds were maintained at about 80% of their respective free-feeding weight through food-deprivation. Water and oyster shell grits were freely available in the home cages.

Apparatus

The experimental chamber was identical to that described earlier [20]. The response keys, 2 cm in diameter and dimly illuminated with white light, were mounted horizontally 10 cm apart on the front panel of the chamber, each key about 19 cm above the chamber floor. The opening of the key

contacts defined the key-pecking response. The minimum force necessary to operate a key was about 15 g. The food magazine was located between the response keys, 4 cm above the floor of the chamber. A reinforcement consisted of a 3-sec access to grain. The chamber was illuminated by a 7.5 W bulb. White noise was present in the chamber at all times and the chamber was ventilated by an exhaust fan. Conventional relay programming and recording equipment, located in a room adjacent to that of the experimental chamber, were used.

Procedure

Discrimination training and testing. After the initial habituation to the experimental chamber the birds were shaped to obtain food by pecking the right hand key on a FR 3 schedule. Once this requirement was met, LSD was given before the sessions and the animals were trained to peck the left key to get food; the right hand key was covered. Such "forced" training with the inappropriate key covered was continued for 20 sessions and the requirement for obtaining grain was increased until the birds had to peck the key 15 times in order to get access to food (FR 15 schedule). Half the number of sessions were preceded by saline and the other half by LSD.

During the free-choice discrimination both response keys were available and the birds had to respond on the appropriate key to produce food. Which key was appropriate depended on whether LSD or saline had been administered 15 min prior to the start of the session. Responses on the inappropriate key had no programmed consequences. Discrimination training followed a single alternation designed (LSD, saline, LSD, saline, etc.) and the birds were trained three times per week (Mondays, Wednesdays and Fridays) for 10 min per session on a FR 15 schedule of reinforcement. The drug training condition (D) consisted of an intramuscular injection of 40 µg/kg of LSD tartrate and the nondrug training condition (N) was 1 ml/kg of saline (0.9%) and the solutions were given 15 min prior to the sessions.

When the pigeons selected the correct key (left or right key), depending on the D or N treatment, at the onset of each training session during at least 8 out of 10 consecutive training days, the animals were switched from the training procedure to the test procedure. The sequence for training under LSD (40 µg/kg for 3 pigeons and 50 µg/kg for one pigeon) or saline (1 ml/kg) on Mondays and Wednesdays and testing (T) on Fridays became D, N, T (Week 1), N, D, T (Week 2), D, N, T (Week 3), etc. Approximately half the number of tests were preceded by a D training session and consequently the remaining tests were preceded by a N training session. During test sessions, except those listed in Table 1·(see below), the pigeons were allowed 10 pecking responses after which the program was switched off and the bird was returned to its home cage, i.e., these tests were conducted under extinction conditions. During the tests listed in Table 1, the pigeons could perform 225 responses during the 10 min period allowed and if all responses were on the selected key, i.e., the key on which the animal first completed 15 responses, a total of 15 reinforcements would have been available (reinforced tests). Once one key was selected, pecking on the other, non-selected key, did not activate the food magazine. All test sessions were preceded by at least one LSD and one saline training session. Test sessions were not conducted unless the performance during the two preceding training sessions had been on the correct key. The experimental period covers about 18 months.
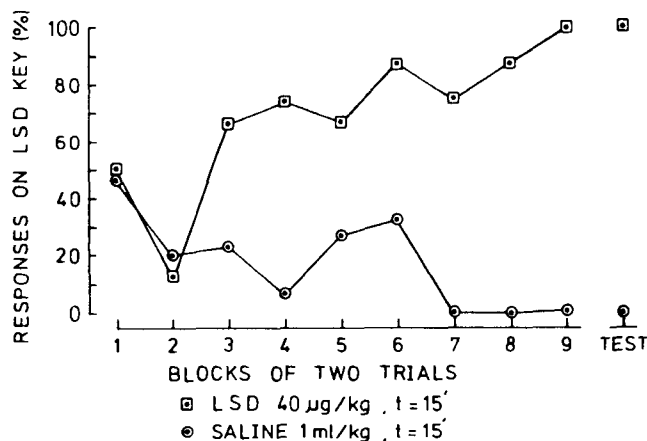

FIG. 1. Acquisition of LSD discrimination in pigeons. The discriminative performance in terms of percentage responses on the LSD associated key for the initial 15 peckings of 4 pigeons required to discriminate between saline and 40 µg/kg of LSD. Injections were given intramuscularly 15 min prior to the sessions. One bird was retrained with 50 µg/kg of LSD (not shown) and therefore the test refers to the performance of 3 birds given 40 µg/kg of LSD and one bird tested with 50 µg/kg of LSD. Tests are based on 10 pecking responses for each pigeon.

Drugs. D-Lysergic acid diethylamide tartrate (LSD, Sandoz: 1701), 2-bromo-D-lysergic acid diethylamide (BOL, 148 HTA, Sandoz: GA.462.469), psilocybin (CY 39, Sandoz: 8001), mescaline hydrochloride (3,4,5-trimethoxyphenethyl amine, Sigma: M-8500), N,N-dimethyltryptamine (DMT, Sigma: D-6129), morphine hydrochloride (ACO), and pentobarbital sodium (Abbott) were dissolved in saline (0.9%). Suspensions of l-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC, U.N. Narcotics Lab. in Geneva: ADL 16792-81) contained 10% propylene glycol, 1% tween-80, and saline [37]. Methergoline, as free base (Farmitalia: 61415), was dissolved in saline with the aid of citric acid. All drug solutions were freshly prepared and injected intramuscularly (IM) in a volume of 1 ml/kg. Doses refer to the forms indicated.

Data analysis. Data are presented as the average percentage of pecking responses on the LSD associated key (LSD key). In the legends the base-line performances are noted and the abbreviations used are explained in the legend of Table 1 (see below). The procedure of Litchfield and Wilcoxon [28] was used to provide estimates of doses yielding 50% LSD associated responses (ED_{50}). Comparisons of rates of responding were computed with the A-test for paired contrasts [30].

RESULTS

The "free-choice" discrimination acquisition curves are shown in Fig. 1. Data, however, do not include sessions where the birds did not respond. This occurred for a total of 5 LSD sessions in two of the birds. Because one of the pigeons performed poorly during the initial test period this bird was retrained with a dose of 50 µg/kg of LSD rather than 40 µg/kg. This one bird needed 11 additional training sessions to once again meet the criterion after which its discrimination performance was well retained during the subsequent test periods.

A calculation of the average number of responses (±SEM) emitted during the 10 min training sessions during test periods showed that the 3 pigeons trained with 40 µg/kg-
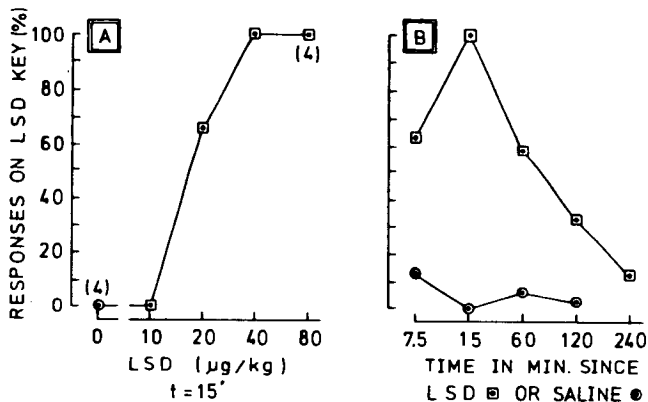
FIG. 2. Dose-response (A) and time-course (B) curves. Pigeons were trained to discriminate between saline (N) and LSD (D). The regular injection training interval was 15 min. Except otherwise indicated data are from 3 pigeons (D=40 μg/kg), each bird performing 10 pecking responses. The fourth pigeon was trained with 50 μg/kg of LSD. Base-line performance for 39 D- and 40 N-training sessions were, respectively (mean ± SEM): FRF: 15.0 (0.0) and 15.5 (0.3); DK selected: 38/39 and 1/40; % RSK: 99.7 (0.2) and 99.2 (0.4); symbols are explained in the legend of Table 1.

of LSD emitted 972.6 (11.5), 743.4 (8.5) and, 826.1 (15.9) responses during the LSD sessions and 974.7 (9.2), 713.2 (7.8) and, 912.2 (15.2) responses during the nondrugged sessions, respectively. The corresponding values for the bird retrained with 50 μg/kg of LSD was D=904.4 (27.7) and N=702.3 (18.5). Statistical comparisons (A-test) between these D- and N-training sessions suggested a significantly increased response output for two of the pigeons, one of which was the bird trained with 50 μg/kg of LSD, during D sessions ($p<0.01$–0.001), no significant difference ($p>0.05$) between D and N sessions in one bird and, finally, a reduced response rate ($p<0.01$) was noted for one bird during the LSD training sessions.

Figure 2 summarizes the results from the tests with various doses of LSD after the constant injection-test interval of 15 min (frame A) and the effects of testing the 40 μg/kg training dose of LSD at various intervals after the injections (frame B). LSD appropriate responding was shown to be dependent both on the dose ($ED_{50}=18$ μg/kg) and the injection-test interval used. A probit analysis of the decrease of LSD responding as a function of time suggested that 50% of LSD responding persists 84 min post-injection. Regardless of the time-interval tested, the vehicle (saline 1 ml/kg) predominantly resulted in responding appropriate for the non-drug associated key.

Tests with psilocybin, 2-bromo-D-lysergic acid diethylamide (BOL), and mescaline are summarized in Fig. 3. All the birds responded on the LSD key after treatments with 3 mg/kg psilocybin. Latency to initiate responding was not appreciably different from the regular LSD training sessions until the 1 mg/kg dose of psilocybin was tested where initiation of responding was delayed by several minutes in two of the birds. A further increase in the delay was observed after the 3 mg/kg dose of psilocybin. None of the doses of BOL tested resulted in a proportion of LSD associated responses comparable to that of the regular LSD training sessions. In tests with 1mg/kg of BOL two of the birds selected the LSD key whereas the two other birds emitted their 10 pecking responses on the non-drug key. The two birds responding after the 3 mg/kg dose of BOL primarily responded on the
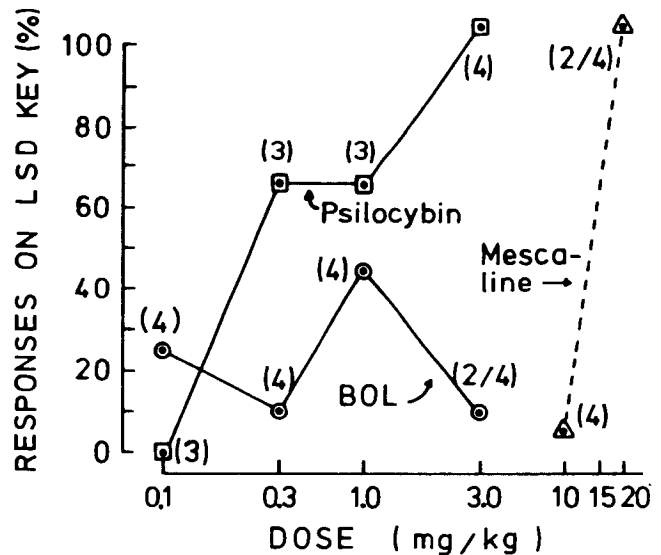

FIG. 3. Substitution tests with psilocybin, 2-bromo-D-lysergic acid diethylamide (BOL) and mescaline. Pigeons were trained to discriminate between saline (N) and LSD (D). Numerals within parenthesis indicate the number of subjects tested, each bird performing 10 pecking responses. Only two out of four pigeons pecked on the keys when tested with the highest doses of BOL and mescaline. Base-line performance for 46 D- and 54 N-training sessions were, respectively (mean ± SEM): FRF: 15.0 (0.0) and 15.0 (0.0); DK selected: 46/46 and 4/54; % RSK: 99.9 (0.5) and 99.6 (0.2); symbols are explained in the legend of Table 1.

saline key as they had done during the preceding test occasions. Latency to initiate responding was delayed after the two higher test doses of the drug in all pigeons except for the one bird trained with 50 μg/kg LSD. All of the four birds tested with 3 mg/kg and 10 mg/kg of mescaline responded mainly on the saline appropriate key. Tests with two higher doses (15 and 20 mg/kg mescaline) resulted in a marked reduction in response output. The two birds whose performance is depicted in the figure performed 5 and 10-keypecking response, respectively, on the LSD key.

Tests for possible antagonism of the LSD induced stimulus responding by methergoline are summarized in Fig. 4. The results suggest a weakened stimulus control of LSD after pretreatments with the two lower doses of methergoline. The two birds responding after the 3 mg/kg dose of methergoline pecked on the LSD key as they had done during the preceding challenge tests.

In Table 1 the results from substitution tests with n,n-dimethyltryptamine (DMT), $Δ^9$-tetrahydrocannabinol ($Δ^9$-THC), morphine and pentobarbital (P-barb) are shown. DMT, 8 mg/kg, substituted for the LSD stimulus whereas the dose of 4 mg/kg resulted in responding on the saline key. Latency to initiate responding was delayed after the higher DMT dose and, one of the four birds did not respond. None of the other test drugs yielded responding above 50% LSD appropriate responses. The higher doses of $Δ^9$-THC (0.50 mg/kg) and morphine (6.0 mg/kg) suppressed responding completely, i.e., none of the animals emitted any keypecking responses during the 10 min test-period allowed.

DISCUSSION

The present study has shown that LSD can be applied as a discriminative stimulus to control differential responding by

pigeons in an operant, two-choice (left vs right key) response selection paradigm. Such a discriminative function of LSD has been described earlier in rats [25] though the absolute dose of LSD used for the training usually have been higher than the dose of 40 to 50 $\mu g/kg$ used in this study.

In pigeons thus trained, psilocybin ($ED_{50}=0.55$ mg/kg) and DMT ($ED_{50}=5.7$ mg/kg) substituted for LSD. Earlier drug discrimination studies in rats suggested that psilocybin ($ED_{50}=0.80$ mg/kg) substituted for 48 $\mu g/kg$ of LSD [36] whereas others [9] reported only 50% LSD appropriate responding when testing 0.8 mg/kg of psilocybin; in the latter study the training dose of LSD was higher (80 $\mu g/kg$). The differences in the training doses of LSD probably explains the discrepancy since ED_{50} values mainly are determined by the training dose used [22,31]. Since DMT generalized to the LSD stimulus in pigeons this drug also is to be incorporated in the category of compounds related to the "psychedelic cue" of which LSD is the prototype drug. The psychedelic potential of DMT is well verified but in contrast to LSD, the psychedelic effects of DMT has a rapid time-course and terminates already after 1 hr [6, 14, 39]. A rapid time-course of DMT on disruption of rat shuttle-box performance [38] and demonstrations of some cross-tolerance between DMT and LSD in rats [24] seem to corroborate the human data.

The significance of the two birds that pecked the LSD key, one of which emitted only 5 responses, after the two higher doses of mescaline (15 and 20 mg/kg) is difficult to evaluate. Cross-generalization between LSD and mescaline is consistently found in rats discriminating between either of the compounds and saline [25]. The effects after the higher doses of mescaline on gross behavior of the pigeons consisted of alternating periods of shaking and immobility and the feathers were ruffled; food offered after the experimental sessions was not ingested immediately as was otherwise the case (see also [15]). These effects of mescaline may obscure a possible common psychedelic cue-component between the
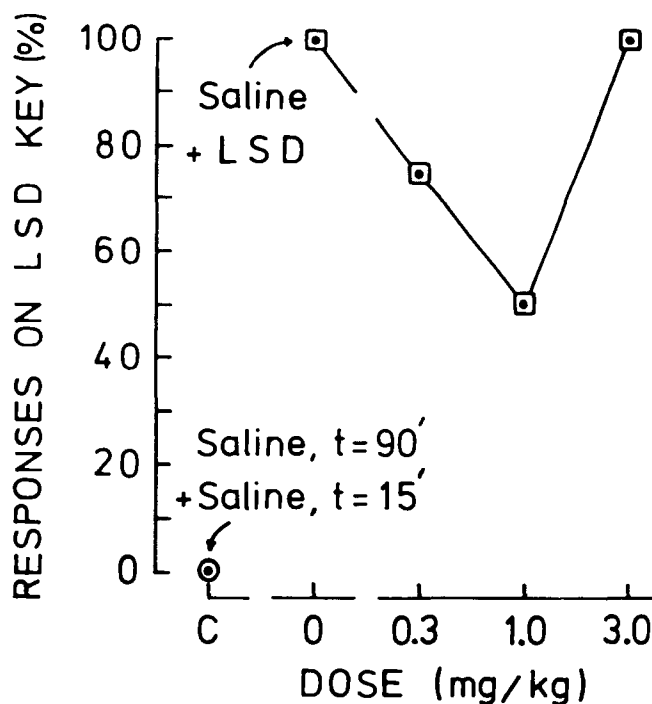

FIG. 4. Tests for antagonism of the LSD stimulus by methergoline. Pigeons were trained to discriminate between saline (N) and LSD (D). An injection of saline or methergoline preceded the administration of LSD, 40 $\mu g/kg$ for 3 birds and 50 $\mu g/kg$ for one bird, by 75 min. Testing occurred 15 min after the LSD injection. One and two birds, respectively, did not peck the keys after the two higher doses of methergoline (1 and 3 mg/kg). All other data points refer to 4 pigeons, each bird performing 10 pecking responses. Baseline performance for 22 D- and 18 N-training sessions were, respectively (mean ± SEM): FRF: 15.0 (0.0) and 15.0 (0.0); DK selected: 21/22 and 1/18; % RSK: 99.6 (0.3) and 99.1 (0.5); symbols are explained in the legend of Table 1.

TABLE 1

SUBSTITUTION TESTS (T) WITH N,N-DIMETHYLTRYPTAMINE AND OTHER PSYCHOTROPIC DRUGS IN FOUR PIGEONS TRAINED TO DISCRIMINATE BETWEEN SALINE (N) AND LSD (D)

Drug	Dose (mg/kg)	Time (min)	n	DK selected	FRF ± SEM	% RSK	% LSD responses
N = saline	—	15	30	0/30	15.0(0.1)	99.8	0.3*
D = LSD	0.04	15	31	31/31	15.3(0.6)	100.0	99.7
T = DMT	4.0	15	4	0/4	15.0(0.0)	100.0	0.0*
T = DMT	8.0	15	4	3/3	16.7(1.1)	100.0	99.3
T = Δ⁹THC	0.25	90	4	0/3	18.7(3.4)	95.4	23.7*
T = Δ⁹THC	0.50	90	3	0/0	—	—	—
T = Morphine	3.0	45	4	0/3	15.0(0.0)	100.0	0.1*
T = Morphine	6.0	45	3	0/0	—	—	—
T = P-barb.	4.0	10	4	0/4	16.5(1.7)	81.0	6.0*
T = P-barb.	8.0	10	4	1/4	16.8(2.0)	84.2	41.6*

*Significantly different from the LSD training scores ($p<0.05$, A-test).

n refers to the number of tests. DK selected refers to the number of tests where responding birds selected the LSD associated key. FRF refers to the mean number (± SEM) of responses needed to produce the first food presentation (possible values 15 to 29). % RSK refers to the mean percentage responding on the selected key out of the total number of pecking responses emitted during a session. % LSD responses refers to the mean number of peckings on the LSD key out of the total number of responses. There were 2 incorrect selections for the 35 D-training sessions and 1 incorrect selection for the 34 N-training sessions for the whole test period. DMT=N,N-dimethyltryptamine; Δ⁹-THC=Δ⁹-tetrahydrocannabinol; P-barb.=pentobarbital sodium.

compounds and before considering a species difference it seems advisable to test LSD also in birds trained to discriminate between mescaline and saline.

None of the doses of BOL tested resulted in a proportion of LSD responding comparable to that of the LSD training dose. A partial LSD-like effect has been noted in man after intake of BOL at 100 times the dose of the parent compound [19]. Single unit cell recordings have shown a partial inhibition of raphé (serotonin) neurons by BOL; LSD and DMT inhibited the firing of all raphé units [1,2]. Thus in high doses BOL seems to share effects with LSD in the CNS but we suggest that the drug-induced stimulus-complexes are only partly interchangeable resulting in the mixed key-selection noted in our pigeons. These data and interpretations do not fit the observations that the addition of BOL slightly attenuates the discriminative control of LSD or quipazine in rats [26,41]. BOL (1.1 mg/kg) tested singly in the quipazine (1 mg/kg) trained rats produced only 14% quipazine appropriate responses. BOL has not been tested singly in rats discriminating between LSD and saline.

Tests with Δ^9-THC, morphine and, pentobarbital resulted mainly in saline associated responding by the birds. Discriminative response control has been demonstrated with these test drugs in pigeons [16, 20, 21, 23, 27] and the results are therefore not due to a lack of intrinsic activity of the test compounds. These data thus attest to the specificity of the LSD induced cue in pigeons and essentially are in accord with previous drug discrimination studies in rats [25].

Methergoline, a potent and fairly selective antagonist of post-synaptic 5-HT receptors [12, 13, 33, 35] was used as a possible antagonist of LSD. However, only a partial blockade was obtained. Except in one instance [18] discriminations based upon psychedelics (LSD or mescaline) in rats have been attenuated by various 5-HT antagonists, notably methiothepin [8, 26, 44]. However, methergoline was not included in these studies.

The data on the decay of LSD responding ($ET_{50}=84$ min) in the present study seem to corroborate the suggestion by Cameron and Appel [9] that the LSD stimulus decays rather rapidly. Out of two rats, one primarily responded on the LSD bar 60 min after an intraperitoneal (IP) injection of the training dose of LSD (80 μg/kg) whereas the other rat responded on the saline bar. Six hours after injections both rats selected the saline bar [9]. LSD disappears from the rat brain 40 to 60 min after IP injections [34] and the disappearance curves for LSD shows a similar decay over time in both naive and tolerant rats [42]. If the cue value of LSD is directly related to the concentration of the drug in brain our results suggest that LSD disappears rapidly also from the pigeon brain. In support for such a possible correlation, Hirschhorn and Rosecrans [17] reported a good correspondence between nicotine levels in various brain areas after different injection-time intervals of the drug and the decay of nicotine-induced discriminative responding.

In conclusion, LSD possesses discriminative effects also in a nonmammalian species and the LSD stimulus thus induced share effects with two other indoleamine psychedelics (DMT and psilocybin). The relationships of the LSD stimulus to the phenethylamine mescaline are inconclusive as are the mechanism of action for the LSD discrimination in pigeons. The LSD stimulus is different from the stimulus-complexes induced by BOL, Δ^9-THC, morphine and, pentobarbital.

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