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Differentiation between the stimulus effects of (+)-lysergic acid diethylamide and lisuride using a three-choice, drug discrimination procedure*

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Abstract. The discriminative stimulus properties of (+)-lysergic acid diethylamide (LSD) and lisuride hydrogen maleate (LHM), were compared in a three-choice, water reinforced (FR 20) situation in which rats were required to press one lever following LSD (0.08 mg/kg), a second lever following LHM (0.04 mg/kg), and a third lever following saline. Reliable drug-appropriate responding was established in 72 sessions. Dose-response tests with LSD and LHM indicated that, as dose increased, the per cent of responding on the lever associated with the particular training drug also increased; little or no cross-transfer occurred between LSD and LHM. In generalization tests, the serotonin (5-HT) agonist quipazine substituted for LSD but not LHM while the dopamine (DA) agonist apomorphine mimicked LHM but not LSD; an unrelated compound, pentylenetetrazol (PTZ), produced responding on the saline-appropriate lever. In combination tests, 5-HT antagonists (e.g., BC-105 and low doses of pirenperone) blocked responding on the LSD lever while DA antagonists (e.g., haloperidol and much higher doses of pirenperone) blocked LHM-appropriate responding. These data suggest that the three-lever (D-D-N) procedure is similar to, but can be more sensitive than the two-lever (D-N) procedure (because it can differentiate between LSD and LHM); they therefore at least partially support the hypothesis that three-choice discriminations can be conceptualized as two separate, two-choice (D-N) discriminations (Jarbe and Swedberg 1982). The results also confirm suggestion that the stimulus effects of LSD and LHM are mediated by different mechanisms; the primary action of LSD is serotonergic (5-HT_2), while that of LHM is dopaminergic (White 1986).

Key words: Dopamine – Drug discrimination – LSD – Lisuride – Serotonin – Three-choice discrimination

Drug discrimination (DD) procedures are helpful in efforts to classify psychoactive drugs on the basis of their perceived (subjective) effects (Barry 1974) and to identify the neuronal mechanisms that underlie these effects (Colpaert and Slangen 1982). This is probably because the findings of many, procedurally different DD experiments have been remarkably consistent over a relatively long period of time and compare favorably with other in vivo assays with respect to their sensitivity and pharmacological specificity (Appel et al. 1982). However, because the results of any discrimination experiment (DD or other) depend on training conditions (Honig and Urcuioli 1981; White and Appel 1982c) it should be possible, at least in principle, to develop even better (e.g., more selective) DD techniques.

In the most frequently used discrimination task, subjects (usually, rats) are trained to make one of two possible responses (press the left lever) following injection of a psychoactive substance (the "training" drug) and to make another response (press the right lever) in the absence of the drug. Such a successive, conditional, drug versus no drug (D-N) discrimination is comparatively easy to learn and typically results in good stimulus control (i.e., orderly, dose-dependent generalization gradients with steep slopes), perhaps because it involves only one stimulus dimension (intensity or dose). However, it is probably less selective than other DD techniques (below).

Animals can sometimes be trained to differentiate between structurally and pharmacologically similar compounds such as (+)-lysergic acid diethylamide (LSD) and lisuride hydrogen maleate (LHM; White and Appel 1982c) by using a two-choice, drug versus drug (D-D) discrimination task. Such differentiation is also possible with the D-N method but appears to require testing with a considerable number of agonists and antagonists in that, more commonly used situation (White and Appel 1982a, b). For this reason, it might be argued that D-D is more *selective* than D-N. However, the D-D procedure may have at least two disadvantages: it usually requires a prolonged training period, during which active substances must be injected almost every day, and it might result in relatively flat generalization gradients (Jarbe and Swedberg 1982; Swedberg and Jarbe 1985; White and Appel 1982c).

Animals can also be taught to discriminate either among three different drugs or doses (D-D-D) or between two

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drugs and the absence of both drugs (D-D-N). From a methodological point of view, the D-D-N procedure is particularly interesting because it combines D-N and D-D and might therefore have some of the advantages of both discrimination tasks (Jarbe and Swedberg 1982; Swedberg and Jarbe 1986). For example, relatively steep generalization gradients (which are often taken to indicate strong stimulus control or sensitivity), similar to those produced by D-N training with appropriate drugs, might also be produced by D-D-N training which has therefore been hypothesized to comprise two separate D-N discriminations that are processed in parallel (Jarbe and Swedberg 1982). While it must not be forgotten that characteristics of generalization gradients always depend on *quantitative* as well as qualitative differences among particular training stimuli or drugs (White and Appel 1982b), the similarities in the shapes of dose-response and test gradients in D-N and D-D-N situations generally support this hypothesis (France and Woods 1985; Leberer and Fowler 1977; Overton 1967; Swedberg and Jarbe 1986; White and Holtzman 1981, 1983). However, since discrimination between two drugs is also involved in D-D-N training, its selectivity might be comparable to that of D-D (above).

The purpose of the present experiment was to assess further some of the chracteristics of the D-D-N paradigm and to explore its use in analyzing the neuronal substrates of two pharmacologically as well as structurally similar drugs LSD (0.08 mg/kg) and LHM (0.04 mg/kg); these substances (and doses) have been studied extensively in this laboratory and have proven to be more difficult to differentiate with D-N than with D-D procedures (above).

Materials and methods

Subjects. Eleven experimentally-naive, male albino rats (Charles River, Sprague-Dawley, Wilmington, MA), weighing approximately 500 g at the beginning of the experiment, were used. They were housed individually with food freely available and access to water restricted to 6–12 h on weekends and 10–15 min per day during the week. This procedure maintained their weights at 80–85% of free-feeding values. The colony was kept at a constant temperature (21–23° C) and humidity (40–50%); lights were on from 7:00 A.M.–7:00 P.M.

Apparatus. The apparatus, with some modifications, has been described elsewhere (Overton 1978). Two identical chambers were constructed from components available in the Psychology Department Shop; each was 24 × 24 × 24 cm square, equipped with steel rod floors and contained a commercially-available dipper, BRS/LVE Model No. SLD-002 (114-90), which delivered 0.1 ml tap water; this was mounted in the center of one wall, 2 cm above the floor. Each chamber was equipped with three levers, BRS/LVE Model No. SLD-003 (121-03), which were mounted 5 cm apart, 6 cm above the floor, on the wall opposite the dipper. Illumination was provided by a 28 V house light positioned 15 cm above the dipper. The chambers were contained in sound-attenuating and light-attenuating enclosures (Coleman picnic/ice chests); blowers provided ventilation as well as masking noise. A MINC-11 computer (Digital Equipment Corporation), located in an adjacent room, was used to control experimental events and to collect data.

Shaping. Subjects were injected IP with saline (0.9% NaCl) and trained by the method of successive approximations, first to drink from the dipper, and then to press the lever under a fixed-ratio (FR 1) schedule of reinforcement. The FR 1 requirement was then increased gradually until all rats were responding reliably under an FR 20 schedule.

The rats were next injected with LSD (0.08 mg/kg), LHM (0.04 mg/kg), or saline (1 ml/kg), 15 min before daily (Mon–Fri) training sessions with a duration of 30 min, during which only the stimulus-appropriate lever was present (left, center or right). Animals received five consecutive LSD sessions, a single saline session, followed by five consecutive LHM sessions. Training was carried out 20 min per day, 5 days per week. To ensure reliable responding, each condition (LSD, LHM or saline) was presented in random order for five additional sessions.

Discrimination training. The three levers were then presented simultaneously. Rats were required to respond on the stimulus-appropriate (correct) lever following each of the three conditions; completion of FR 20 on the inappropriate lever was followed by a time out of 1 min during which no reinforcers were delivered and the house light was turned off. The two drugs and saline were administered in a random order with the restriction that no condition be presented for more than three consecutive sessions. Lever position was randomized to control for the development of position cues based on olfactory stimuli (Extance and Goudie 1981). During this phase of the experiment, two rats exhibited severe response suppression following LHM and were therefore removed from the study.

Testing procedure. After stable and reliable discrimination performances (mean individual accuracies of at least 80% correct for ten consecutive training sessions) were demonstrated by all remaining animals ($N=9$), testing began. That is, for the remainder of the experiment, daily (LSD, LHM or saline) sessions were programmed according to a table of permutations, so that any of the three experimental conditions was equally likely to precede a test session (LSD-LHM-SAL; LHM-LSD-SAL; SAL-LHM-LSD; LHM-SAL-LSD; LSD-SAL-LHM; SAL-LSD-LHM). At the completion of each sequence, animals that met a criterion of at least 80% correct for each of the three conditions were tested. During these sessions, rats were placed into the chambers as during training; however, once the 20 responses were completed on any of the three levers or the session time elapsed (30 min), the house light was turned off and the animal was removed from the chamber without reinforcement; thus, extinction conditions were in effect. Four types of tests were given: 1) *Dose-Response tests* with various doses of LSD or LHM; 2) *Substitution tests* with various "novel" drugs including putative DA and 5-HT agonists and antagonists and an unrelated anxiogenic and convulsant compound, pentylenetetrazol (PTZ); 3) *Combination tests* with putative DA or 5-HT antagonists and; 4) *Control tests,* for possible residual effects of drugs given on the previous day. Following test sessions, the animals were given 10–15 min access to water.

Drugs. Although all animals were given the same tests on any given day, the order in which drugs and doses were tested was randomized throughout the experiment. All compounds were prepared each day in deionized water and

were injected IP in a volume of 1.0 ml/kg. Doses of the following drugs (supplier; injection test interval) refer to the weights of the salts: apomorphine HCl (Sigma; 15 min), BC-105 maleate (Pizotifen, Sandoz; 15 min), lisuride hydrogen maleate (LHM, Schering, 60 min), (+)-lysergic acid diethylamide bitartrate (LSD, NIDA; 15 min), pentylenetetrazol (PTZ, Sigma; 15 min), and quipazine maleate (Miles; 15 min). Doses of haloperidol (McNeil; 60 min) and pirenperone (Janssen; 60 min), which were diluted with deionized water from ampules provided by the suppliers, refer to the free bases.

Data analysis. During training, accuracy was defined as the percentage of correct responses appropriate to the training condition to total responses before the delivery of the first reinforcer; during test sessions, accuracy was the percentage of LSD-, LHM- or saline-lever responses to the total number of responses. Response rates (responses per min) were also evaluated during training and test sessions. For training sessions, the rate of responding was calculated as the total number of responses emitted before completion of the first FR 20 divided by the number of minutes taken to complete the first ratio. During test sessions, the rate was calculated as either the number of minutes taken to complete 20 responses or 30 min if 20 responses were not completed.

Student's *t*-tests for repeated measures were used to compare the previous performance (or response rates) on LSD, LHM and saline sessions with performance on all test compounds. In order to ascertain possible training drug (LSD or LHM) effects on testing performance, a repeated measures analysis of variance (ANOVA) was used to compare performance on the immediately preceding condition to performance obtained under a particular dose of a test compound. Acquisition performance (per cent correct) and response rates (responses per min) were also analyzed using a repeated measures ANOVA. All comparisons were made with Type I error rate (alpha) set at 0.05.

Results

Acquisition

All animals learned to discriminate among the three training drugs. The mean number of sessions to criterion (independent of condition) was 72 (SEM = ±4); accuracy (per cent correct) did not differ significantly as a function of drug ($F_{2,26} = 2.72$, $P < 0.08$). Additional training during sessions 61–72 further increased per cent correct to 92±2 following LSD, 93±1 following LHM, and 95±2 following control injections. Mean response rates (Rs/min) did not differ significantly across training conditions: LSD = 39±3, LHM = 35±3, saline = 37±2 ($F_{2,44} = 0.596$, $P < 0.56$).

Dose-response tests

Dose-response curves for the two training drugs are shown in Fig. 1. Both sets of data are drug and dose dependent. That is, following treatment with increasing doses of LSD (solid lines, closed triangles), per cent of responding on the LSD-appropriate lever increased (left panel); 0.08 and 0.16 mg/kg LSD produced levels of drug-appropriate responding that did not differ from those observed on previous LSD training sessions (and thus could be said to substitute for the training dose). As dose of LSD increased, responding on the saline-appropriate lever (broken lines, open circles) decreased monotonically; very few responses occurred on the LHM lever (closed squares) after *any* dose of LSD.

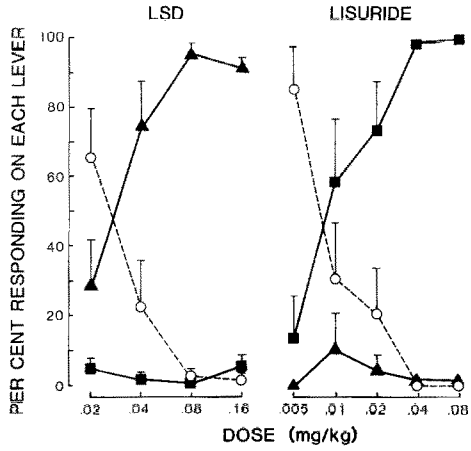

Fig. 1. Results of dose-response tests with LSD (*left panel*) and lisuride (*LHM; right panel*) in rats ($N = 9$) trained to discriminate LSD (0.08 mg/kg) from LHM (0.04 mg/kg) from saline. *Solid lines, closed triangles* (▲—▲) denote per cent responding on the LSD-appropriate lever, *solid lines* with *closed squares* (■—■) denote responding on the LHM-appropriate lever, and *broken lines* with *open circles* (o--o) denote responding on the saline-appropriate lever, during test sessions. All points are means (±SEM) of eight or nine subjects which completed at least 20 responses on any one of the three levers

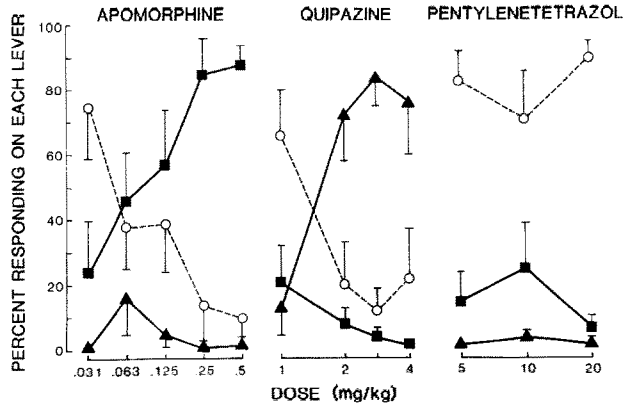

Fig. 2. Results of substitution (generalization) tests with apomorphine (*left panel*), quipazine (*center panel*) and pentylenetetrazol (*right panel*) in rats trained to discriminate LSD (0.08 mg/kg) from LHM (0.04 mg/kg) from saline. Symbols as in Fig. 1

Similar effects occurred following tests with lisuride (right panel). That is, as the dose of the test drug increased, responding on the LHM-appropriate lever (solid lines, closed squares) increased while responding on the saline-appropriate lever (open circles) decreased; little, if any, responding occurred on the LSD-appropriate lever. The amount of responding on the LHM-appropriate lever after 0.04 and 0.08 mg/kg of LHM did not differ from amounts observed during previous training sessions with 0.04 mg/kg of this compound.

Table 1. Results of substitution tests with apomorphine (0.25 mg/kg) and quipazine (2 mg/kg) following each training drug

Previous training drug	Test compound	Lever selected	Per cent[a] responding	Rate[b] (*R*'s/min)	*n*/*N*[c]
LSD	Apomorphine	LHM	86± 7	6± 2	8/8
LHM	Apomorphine	LHM	90± 6	42±21	8/8
Saline	Apomorphine	LHM	81±12	10± 5	8/8
LSD	Quipazine	LSD	68±18	19± 5	7/7
LHM	Quipazine	LSD	63±17	7± 2	7/7
Saline	Quipazine	LSD	77±13	13± 5	7/7

[a] Mean percentage of responses completed on the most frequently chosen lever (±SEM) during the test session
[b] Mean number of responses (*R*'s/min, ±SEM) during the test session
[c] *n*/*N*: number of animals (*n*) completing 20 responses on either lever/number of animals tested (*N*)

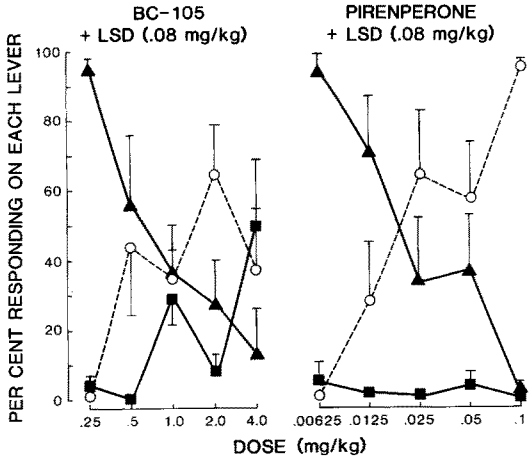

Fig. 3. Results of combination tests with pizotifen (BC-105; *left panel*) and pirenperone (*right panel*) given prior to LSD (0.08 mg/kg) in rats trained to discriminate LSD from LHM from saline. Symbols as in Fig. 1

Substitution tests

Apomorphine (left panel), dose-dependently mimicked LHM but not LSD (Fig. 2); that is, as the dose of this DA agonist increased, responding increased on the LHM lever, and decreased on the saline lever; very little responding occurred on the LSD lever. Significant amounts of LHM-appropriate responding occurred following 0.25 and 0.5 mg/kg of apomorphine.

Quipazine (center panel) mimicked LSD but not LHM. The maximal effect (84% ±8) occurred at a dose of 3.0 mg/kg; higher doses of this 5-HT agonist produced behavioral disruption in some animals. However, the per cent responding on the LSD-appropriate lever following doses of 2.0, 3.0 or 4.0 mg/kg of quipazine did not differ from those obtained during previous LSD training sessions.

Saline-appropriate responding occurred following treatment with pentylenetetrazol (right panel); that is, this substance did not mimic either LSD or LHM at the doses tested (per cent responding was different from both LSD and LHM training sessions, but not from previous saline sessions).

To explore the possibility that the drug given on the day *preceding* a substitution test might affect the extent of generalization *during* the subsequent test, the effects of 0.25 mg/kg of apomorphine and 2.0 mg/kg of quipazine were reassessed following each of the training conditions (LSD, LHM and saline; Table 1). Neither the substitution of apomorphine for LHM ($F_{2,14}=0.246$, $P<0.787$) nor that of quipazine for LSD ($F_{2,12}=0.328$, $P<0.73$) depended on this variable.

Combination tests

When tested in combination with LSD (0.08 mg/kg), BC-105 reduced amount of responding on the LSD-appropriate lever in a dose-dependent manner (Fig. 3, left panel); the lowest amount (following 4.0 mg/kg of BC-105+0.08 mg/kg LSD) was not different from saline. Interestingly, as this "antagonism" occurred, the per cent of alternative choices was divided between the LHM and saline levers. However, combinations of the highest and most effective dose of BC-105 (4.0 mg/kg) and saline engendered respond-

Table 2. Results of tests in which with receptor antagonists were given in combination with LSD (0.08 mg/kg), LHM (0.04 mg/kg) or saline

Test	Dose (mg/kg)	Time (min)	Lever selected	Per cent[a] responding	Rate[b] *R*'s/min	*n*/*N*[c]
Saline	–	15	Saline	95± 2	22± 6	8/8
LSD	0.08	15	LSD	96± 3	41±21	8/8
LHM	0.04	15	LHM	99± 1	47±18	9/9
BC-105 (+saline)	4.0	60	Saline	85±12	24± 7	7/8
BC-105 (+LHM)	4.0	60	LHM	97± 3	27±11	6/6
Haloperidol (+saline)	0.25	60	Saline	86± 6	20± 6	6/6
Haloperidol (+LSD)	0.25	60	LSD	88± 8	38± 9	9/9
Pirenperone (+saline)	0.5	60	Saline	81± 5	32± 5	6/6

[a] Mean percentage of responses completed on the most frequently chosen lever (±SEM) during the test session
[b] Mean number of responses (*R*'s/min, ±SEM) during the test session
[c] *n*/*N*: number of animals (*n*) completing 20 responses on either lever/number of animals tested (*N*)

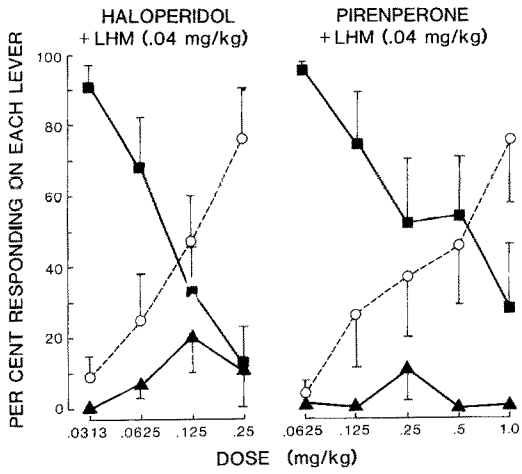

Fig. 4. Results of combination tests with haloperidol (*left panel*) and pirenperone (*right panel*) given prior to LHM (0.04 mg/kg) in rats trained to discriminate LSD from LHM from saline. Symbols as in Fig. 1

ing on the saline lever and combinations of BC-105 (4.0 mg/kg) and LHM (0.04 mg/kg) failed to alter LHM-appropriate responding (Table 2). In addition, combinations of 8 mg/kg of BC-105 + 0.08 mg/kg LSD (data not shown) also reduced LSD-appropriate responding (to 13%).

Pirenperone proved to be a more effective antagonist of LSD (Fig. 3, right) than BC-105 in that this substance not only dose-dependently reduced responding on the LSD-appropriate lever, but completely eliminated such responding at the highest dose tested (0.1 mg/kg). Moreover, as LSD-appropriate responding decreased, the per cent of saline-, but not LHM-appropriate responses increased; indeed, no responses occurred on the LHM lever after combinations of pirenperone and LSD. Statistically significant antagonism of LSD occurred following doses of 0.025–0.10 mg/kg of pirenperone (+0.08 mg/kg LSD).

When given in combination with 0.04 mg/kg of LHM (Fig. 4; right panel), pirenperone also antagonized LHM but this effect did not occur until the dose reached 1.0 mg/kg, 10 times the dose that completely blocked LSD. Given alone (in combination with saline) pirenperone (0.5 mg/kg) induced responding on the saline-appropriate lever (Table 2).

Haloperidol (in combination with 0.04 mg/kg of LHM) dose-dependently antagonized the stimulus effects of LHM (Fig. 4; left panel) but not LSD (Table 2). As the per cent of LHM-appropriate responding decreased, saline-appropriate responding increased; few responses occurred on the LSD lever. When given alone (in combination with saline) 0.25 mg/kg of haloperidol did not mimic either LSD or LHM (Table 2).

Discussion

The results indicate that the three lever (D-D-N) procedure has several interesting properties that make it particularly useful for the analysis of the in vivo effects of pharmacologically similar compounds. The fact that accuracy of discrimination under each of the training conditions exceeded 90% and remained stable for the duration of the experiment demonstrates that the procedure is *reliable* and *robust;* in addition, the relatively low doses that were discriminated (0.08 mg/kg LSD and 0.04 mg/kg LHM) shows that it is *sensitive* (Appel et al. 1982). Indeed, the D-D-N discrimination may be both more efficient than, and superior to any of the techniques used previously to analyze the stimulus effects of LSD and LHM (Cunningham and Appel 1987; Cunningham et al. 1987; White and Appel 1982a, b). It produces dose-response, substitution and combination test gradients that have relatively steep slopes, similar to those that occur following separate two-choice (D-N) discriminations (Jarbe and Swedberg 1982) and it does so efficiently, in a single group of animals.

The D-D-N task also appears to be at least as *selective* as two-choice procedures. That is, under the conditions of the present experiment, responding occurs on the lever associated with LSD in a dose-related manner following treatment with quipazine and on the LHM lever following apomorphine; neither LSD nor LHM have effects that generalize to compounds such as PTZ which are not known to act through either serotonergic or dopaminergic mechanisms. These observations, coupled with the results of combination tests, in which serotonergic (5-HT_2) antagonists such as relatively low doses of pirenperone and BC-105 blocked the effects of LSD but not LHM while DA antagonists such as high doses of pirenperone and haloperidol blocked LHM but not LSD, support the hypothesis that these substances have discriminably different subjective effects (White and Appel 1982c) as well as mechanisms of action (White 1986; White and Appel 1982a, b).

Thus, although it may be time consuming to implement (though not in comparison to the time it takes to train two, separate two-choice discriminations), the three-choice (D-D-N) procedure is at least as reliable, robust, sensitive, and selective as other DD procedures. A more subtle advantage of the D-D-N method concerns the effects of the third alternative. This is particularly clear in attempts to block the effects of different training drugs with selective antagonists, for example opiates with naltrexone (White and Holtzman 1981) or hallucinogens with BC-105 (above); such antagonism is sometimes inconsistent in two-choice, D-N experiments. In the present instance, blockade of LSD by BC-105 may have occurred because of the presence of the LHM-appropriate lever on which the animal responded following higher doses of BC-105 (in combination with LSD). It is not unreasonable to suppose that these combinations reduced the serotonergic properties of LSD, which normally overshadow other effects of the drug, and thereby allowed dopaminergic aspects of the LSD stimulus complex to emerge (Appel et al. 1982). Similar effects occurred when pirenperone was tested in combination with LHM, although this is less surprising, since high doses of pirenperone have been shown to attenuate the stimulus effects of other DA agonists including lergotrile (Cunningham et al. 1984) and amphetamine (Callahan and Appel, unpublished observations).

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References

Appel JB, White FJ, Holohean AM (1982) Analyzing mechanism(s) of drug action with drug discrimination procedures. Neurosci Biobehav Rev 6:529–536

Barry III H (1974) Classification of drugs according to their discriminable effects in rats. Fed Proc 33:1814–1824

Colpaert FC, Slangen JL (eds) (1982) Drug discrimination. Applications in CNS pharmacology. Elsevier/North-Holland Biomedical Press, Amsterdam

Cunningham KA, Appel JB (1987) Neuropharmacological reassessment of the discriminative stimulus properties of *d*-lysergic acid diethylamide (LSD). Psychopharmacology 91:67–73

Cunningham KA, Callahan PM, Appel JB (1984) Discriminative stimulus properties of lergotrile. J Pharmacol Exp Ther 230:47–52

Cunningham KA, Callahan PM, Appel JB (1987) Discriminative stimulus properties of lisuride revisited. Involvement of dopamine D_2 receptors. J Pharmacol Exp Ther 241:147–151

Extance K, Goudie AJ (1981) Inter-animal olfactory cues in operant drug discrimination procedures in rats. Psychopharmacology 73:363–371

France CP, Woods JH (1985) Opiate agonist-antagonist interactions. Application of a three-key drug discrimination procedure. J Pharmacol Exp Ther 234:81–89

Honig WK, Urcuioli PJ (1981) The legacy of Guttman and Kalish (1956) Twenty-five years of research on stimulus generalization. J Exp Anal Behav 36:405–445

Jarbe TUC, Swedberg MDB (1982) A conceptualization of drug discrimination learning. In: Colpaert FC, Slangen JL (eds) Drug discrimination. Applications in CNS pharmacology. Elsevier/Biomedical Press, Amsterdam, pp 327–341

Leberer MR, Fowler SC (1977) Drug discrimination and generalization in pigeons. Pharmacol Biochem Behav 7:483–486

Overton DA (1967) Differential responding in a three choice maze controlled by three drug states. Psychopharmacologia 11:376–378

Overton DA (1978) Influence of training compartment design on performance in the two-bar drug discrimination task: a methodological report. In: Colpaert FC, Rosecrans JA (eds) Stimulus properties of drugs: ten years of progress. Elsevier/North Holland Biomedical Press, Amsterdam, pp 265–278

Swedberg MDB, Jarbe TUC (1985) Drug discrimination procedures: roles of relative stimulus control in two-drug cases. Psychopharmacology 86:444–451

Swedberg MDB, Jarbe TUC (1986) Drug discrimination procedures: Differential characteristics of the drug A vs drug B and the drug A vs drug B vs no drug cases. Psychopharmacology 90:341–346

White FJ (1986) Comparative effects of LSD and lisuride: clues to specific hallucinogenic drug actions. Pharmacol Biochem Behav 24:365–379

White FJ, Appel JB (1982a) Training dose as a factor in LSD-saline discrimination. Psychopharmacology 76:20–25

White FJ, Appel JB (1982b) The role of dopamine and serotonin in the discriminative stimulus effects of lisuride. J Pharmacol Exp Ther 221:421–427

White FJ, Appel JB (1982c) LSD and lisuride: differentiation of their neuropharmacological actions. Science 216:535–537

White JM, Holtzman SG (1981) Three-choice drug discrimination in the rat: morphine, cyclazocine and saline. J Pharmacol Exp Ther 217:254–262

White JM, Holtzman SG (1983) Three-choice drug discrimination: phencyclidine-like stimulus effects of opioids. Psychopharmacology 80:1–9

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