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An Analysis of Some Discriminative Properties of *d*-Amphetamine

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Abstract. Male albino rats were trained and tested on a two-lever discrimination task based upon the presence or absence of *d*-amphetamine (1.0 mg/kg). This compound was found to produce strong discriminative cues (i.e., 90% correct choice behavior). A dose-effect function was then ascertained and the discriminative ED_{50} (following training with 1.0 mg/kg) was found to be 0.23 mg/kg *d*-amphetamine.

In order to determine the effective duration of *d*-amphetamine action, the interval between injection and testing was varied; it was found that the discriminative effects of the drug began to dissipate between 60 and 90 min post-injection.

In an attempt to compare the discriminative cues of other drugs with those of *d*-amphetamine, injections of LSD (0.04 and 0.08 mg/kg), psilocybin (0.50 and 1.0 mg/kg), THC (0.50 and 1.0 mg/kg), mescaline (5.0 and 10.0 mg/kg), and caffeine (6.0 and 20.0 mg/kg) were given during extinction. In all cases, the rats responded predominantly on the saline-related lever. Only methamphetamine (1.0 mg/kg) produced *d*-amphetamine-like responding.

Finally, alpha-methyl-para-tyrosine (AMPT), a compound which depletes brain catecholamines (CA), was found to disrupt the *d*-amphetamine-saline discrimination.

Key words: *d*-Amphetamine — CNS Stimulants — Discrimination — State-Dependent Learning — Hallucinogenic Drugs — Δ^9-THC.

The behavioral effects of most drugs fall on a dose-related continuum which ranges from little measurable disruption to toxicity. Aside from these presumably unconditioned influences, drugs, like other (external) stimuli (e.g., lights or tones), can acquire the ability to act as discriminative cues which set the occasion for differential behavior. Indeed, a large number of compounds have been classified in terms of the degree of such control they can acquire over behavior (Overton, 1973). In general, it appears that if a drug (D) state is sufficiently different from non-drug (ND) state, or from another drug state, it can be used as a discriminative stimulus or to produce state-dependent learning (SDL) (Overton, 1964). The relative difference between any 2 D states then determines the degree to which differential responding can be maintained. In general, the greater the difference, the stronger the differential control; the more similar the states, the weaker the control. Examples of drugs which produce SDL and which have strong discriminative properties are anesthetics such as pentobarbital (Overton, 1964, 1968; Bliss, 1971), alcohol (Kubena and

Barry, 1969a; Barry and Kubena, 1972), and at least some hallucinogens (Cameron and Appel, 1973; Hirschhorn and Winter, 1971). The opiates (Rosecrans *et al.*, 1973; Hill *et al.*, 1971) and antimuscarinics (Overton, 1966; Kubena and Barry, 1969b) produce moderate control over choice behavior, whereas phenothiozines exert weak or no control (Stewart, 1962).

The purpose of the present experiment was to analyze some of the discriminative properties of one compound, *d*-amphetamine, which is known to exert moderate to strong stimulus control over choice behavior (Harris and Balster, 1971; Overton, 1973; Schechter and Rosecrans, 1973), and to describe a technique for studying this behavior which has certain advantages over those used by other investigators (Harris and Balster, 1971; Cameron and Appel, 1973). The present technique (1) is convenient because complcte extinction does not occur during test periods when novel drug, dose, or temporal parameters are tested, and retraining is therefore unnecessary (Harris and Balster, 1971), (2) prevents the occurrence of any discrimination between training and testing sessions (Cameron and Appel, 1973) and (3) produces response rates which are neither too high nor too low, thus enabling the testing of both rate-depressing and rate-increasing drugs.

Methods

Six experimentally naive male rats (Sprague-Dawley), weighing between 280—350 g, were used in all phases of the experiment. They were approximately 120 days old at the start of experimentation, and were maintained at 80% body weight by restricting water intake to 5 min each day. They were housed individually in a room of constant temperature (75° F) and humidity (40—50%) and maintained on a 12-hr (8:00 a.m. to 8:00 p.m.) day-night cycle with *ad libitum* food. The animals were run at the same time each day, 5 days a week.

Three commercially available experimental chambers (Lehigh Valley Electronics, Model No. 1316) contained in sound-proof, ventilated enclosures were used for training and testing. Each box contained two levers on the front panel separated by a liquid feeder. Each reinforcement consisted of 0.01 ml of tap water; sessions were $^1/_2$ hr long. Electromechanical programming and recording equipment was located in an adjacent room.

Acquisition of the d-Amphetamine-Saline Discrimination. All rats were trained to perform at stable rates on a tandem variable interval 1 min fixed ratio 10 (Tand VI 1 FR 10) schedule with a reset (punishment) contingency added to the FR component. Rats were first shaped to bar-press on a continuous reinforcement schedule on one lever and then on the other, with the first lever removed. On any given day, only one lever was available to avoid presenting the rats with a choice before differential cues (drug injections) were presented. Simultaneously, the reinforcement requirement was gradually raised from CRF to FR 10. The VI component was then introduced such that the animal eventually had to emit 10 responses after an average interval of 1 min had elapsed to obtain water reinforcement (i.e., Tand VI 1 FR 10). Finally, a punishment contingency was added to the FR component in order to prevent superstitious chaining from the incorrect to the correct lever. Thus, following each VI 1, 10 consecutive correct responses were necessary for reinforcement. An incorrect response during the FR sequence reset the stepper so that another 10

responses on the correct lever were required for reinforcement. Both levers were available to the rat only after drug-choice training was begun.

In order to minimize possible systematic effects of position preference, the subjects were randomly divided into 2 groups, 3 rats per group. For 1 group, appropriate responding on the left lever after *d*-amphetamine injections (1.0 mg/kg) was reinforced, whereas the other group was required to respond on the right lever after *d*-amphetamine for reinforcement. The opposite lever was reinforced for each group, respectively, after saline (1.0 ml/kg). The D and ND injections were given 30 min before testing. They were administered randomly with the restriction that the same solution not be given more than 3 days in succession.

Generalization of the d-Amphetamine Cue to Different Doses of Amphetamine. At the conclusion of the first phase (acquisition) of the experiment, the animals were given 2 injections each of 0.0625, 0.125, 0.25, 0.50, and 2.0 mg/kg of *d*-amphetamine in random order. All injections were given $^1/_2$ hr before testing. To prevent further learning, the rats were run on 5-min extinction periods on days when test doses were administered. All test days were preceded by a saline training day to ensure that any residual drug would not influence test dose results. A *d*-amphetamine (1.0 mg/kg) training day was given once a week. Thus, during any week, test doses were usually given on Tuesdays and Fridays, with saline days on Mondays and Thursdays, and *d*-amphetamine days on Wednesdays.

Temporal Parameters of the d-Amphetamine Cue. The rats were injected with 1.0 mg/kg of *d*-amphetamine and returned to their home cages for 60, 90, 120, and 150 min before being tested for lever choice in extinction. All rats were run twice at each time delay. As before, retraining trials (30 min) were interspersed between test days to provide an index of the strength of the original discrimination.

Lever Choice after Novel Test Drugs: Tests for Similarity to d-Amphetamine. The behavioral procedures remained the same. Test drugs and doses chosen (in mg/kg) were psilocybin (0.5 and 1.0), Δ^9-THC (0.5 and 1.0), mescaline (5.0 and 10.0), LSD (0.04 and 0.08), methamphetamine (1.0) and caffeine (6.0 and 20.0). Each test drug dose was chosen from ranges shown to be effective in controlling differential responding (Overton, 1973; Cameron and Appel, 1973). Again, test drug sessions were preceded by a retraining session with saline and *d*-amphetamine retraining days following test drug days. The test drugs were administered in random order.

Effects of Alpha-Methyl-Para-Tyrosine on the d-Amphetamine-Saline Discrimination. AMPT, in powder form, was dissolved in wet mash to a concentration of 200 mg/kg and was fed to the water-deprived rats. Before AMPT administration, the dose effect curve for *d*-amphetamine was re-determined using the same procedure as before. Fifteen hrs after AMPT, when the behaviorally disruptive effects of AMPT are no longer evident, but when brain NE levels remain depleted to approximately 40% of controls (Appel *et al.*, 1970), the rats were given 1 injection of 0.50 mg/kg of *d*-amphetamine; they were tested for lever preference during extinction 30 min later.

Drugs. Dextro-amphetamine sulfate (K & K Laboratories, Plainview, N. Y.) was dissolved in 0.9% sodium chloride and 0.9% benzyl alcohol in distilled water to a concentration of 1.0 mg/ml.

The Δ^9-THC, psilocybin and LSD were obtained from the NIMH Center for Studies of Narcotic and Drug Abuse. Δ^9-THC arrived in 25 mg vials dissolved in 25 ml of absolute alcohol. To remove the alcohol, the contents of each vial were subjected to vacuum until the alcohol evaporated. The brown resinous substance left behind was then suspended in 0.5 ml Triton-X-100 and this suspension was diluted with the required volume of bacteriostatic saline to reach a concentration of 1.0 mg/ml of THC. Psilocybin, in powder form, was weighed and dissolved in 0.9% saline to a concentration of 1.0 mg/ml. LSD, in ampule form (0.1 mg/ml), was diluted

to a concentration of 0.04 mg/ml with saline. Mescaline sulfate powder (Sigma Chemicals, St. Louis), was dissolved in saline to a concentration of 5.0 mg/ml. Methamphetamine hydrochloride (Sigma) and caffeine (Sigma) were generously supplied by Doctors D. A. Powell and L. Milligan of the Neuroscience Research Laboratory, Veterans Administration Hospital, Columbia, South Carolina. The methamphetamine was diluted with saline to a concentration of 1.0 mg/ml and the caffeine was diluted to a concentration of 20 mg/ml.

The AMPT was purchased from Merck, Sharpe, and Dohme, Inc., Rahway, N. J. It was administered orally, in wet mash, in a concentration of 200 mg/kg. All other drugs were injected intraperitoneally, in volumes of 1 ml/kg.

Results

Acquisition of the d-Amphetamine-Saline Discrimination. Fig. 1 shows the acquisition of the *d*-amphetamine-saline discrimination. Data points are based on extinction responding each day. Choice responding (per cent correct) for the first 13 days of training was erratic and fluctuated around the random level. Accuracy improved if the same drug state existed for several successive days and large decreases in accuracy were seen when the drug state changed (D-ND or ND-D). After Day 13, the per cent correct reached 75% and continued to increase until, by Day 40, responding after D and ND reached about 88% correct. Responding on the appropriate lever during days 20—25 was significantly greater than 80% correct ($t = 2.848$, $df = 5$, $P < 0.025$). A repeated measures analysis of variance on these data revealed a significant days effect ($F = 6.317$, $df = 7, 35$, $P < 0.001$). Response rates after *d*-amphetamine were significantly higher than response rates after saline (46 resp/min after *d*-amphetamine and 28 resp/min after saline; $P < 0.0005$, correlated t); this rate differential remained consistent throughout the experiment.

Generalization of the d-Amphetamine Cue to Different Doses of Amphetamine. Fig. 2 shows the per cent responding on the *d*-amphetamine lever after each test dose. Doses smaller than the training dose (1.0 mg/kg) resulted in a smaller percentage of responding on the D lever. At 0.50 mg/kg the animals responded correctly 75% of the time. After 0.25 mg/kg, choice responding was random (53% on the *d*-amphetamine lever). After 0.125 and 0.0625 mg/kg the animals responded primarily on the saline lever (70 and 77%, respectively). Choice responding after 2.0 mg/kg was similar to choice behavior after the training dose, producing 81% responding on the D lever. By converting the doses which "bracketed" the 50% response to log doses and connecting them in a linear function (Barry, 1974) the *d*-amphetamine ED_{50} was estimated as 0.23 mg/kg. Performance on retests of the original discrimination task remained consistent with 82% appropriate responding after 1.0 mg/kg of *d*-amphetamine and 87% after saline.

The Temporal Parameters of the d-Amphetamine Cue. Fig. 3 presents the per cent responding on the *d*-amphetamine lever as a function of time

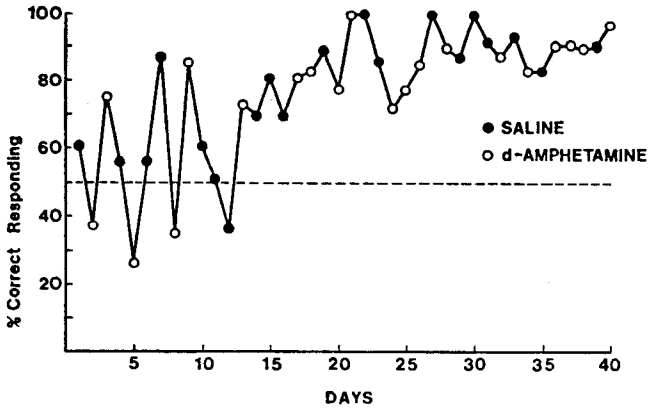

Fig. 1. Per cent correct responding during extinction after 1.0 mg/kg of *d*-amphetamine or saline. Either solution was administered 30 min before the session in random order. Each point represents the average of 6 scores

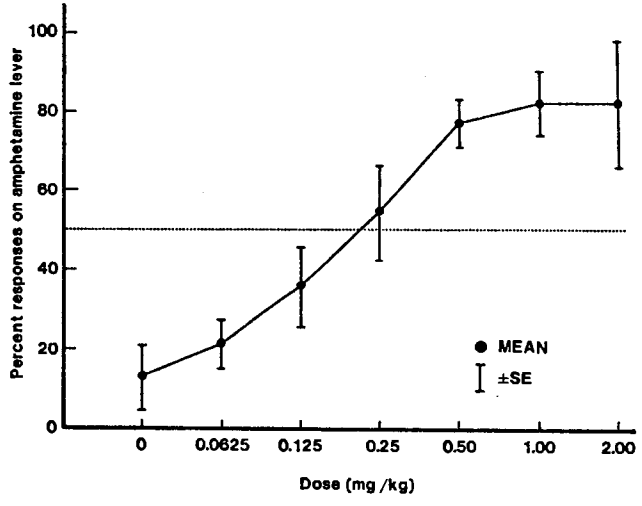

Fig. 2. Per cent responding on the *d*-amphetamine lever as a function of dose. Each novel dose was given twice to all rats in a random order and all injections were given 30 min before the session. Each point represents the average of 12 scores

after injection. After a 60 min delay, 74% of all responding was on the D lever. When the animals were tested 90 min post-injection, responding was about equally distributed on both levers, i.e., random. After a 120 min lapse between injection and testing the rats chose the D lever 33% of the time and after 150 min, responding on the D lever was only 14%. Retraining trials with the normal 30 min latency again produced 94% correct responding after *d*-amphetamine.

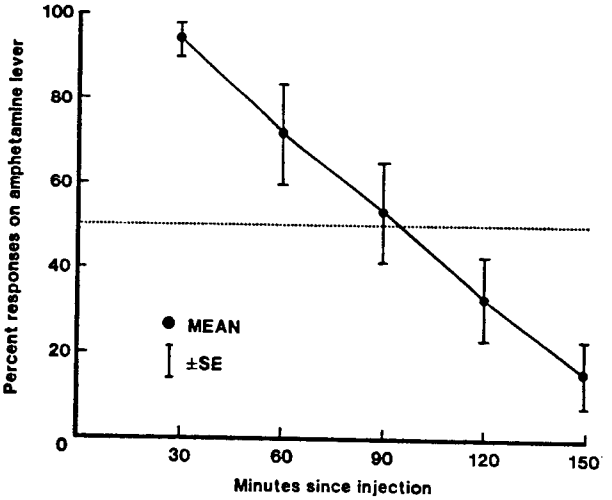

Fig. 3. Per cent of total responding on the *d*-amphetamine lever as a function of minutes since injection. Rats were returned to home cages after injections for the allotted time before testing was carried out. All rats were tested twice at each time delay. Each point represents the average of 12 scores

Lever Choice After Novel Test Drugs: Tests for Similarity to d-Amphetamine. Per cent responding on the *d*-amphetamine lever following each test drug is presented in Table 1. Psilocybin, at doses of 0.5 and 1.0 mg/kg was administered twice to all rats and average per cent responding was only 27 and 23% on the D lever, following each dose respectively. LSD resulted in approximately the same quantitative effect as psilocybin, producing 22.3 and 32.7% responding on the D related lever after 0.08 and 0.04 mg/kg, respectively. One mg/kg of THC resulted in 2% responding on the D lever; after 0.5 mg/kg of THC, responding was 3% on the D lever. Response choice after 5.0 mg/kg of mescaline was 11% to the D lever whereas, after 10% mg/kg of mescaline, responding was entirely on the ND lever. Caffeine, at 20.0 mg/kg, produced random choice responding and, after 6.0 mg/kg, 99% of all responding was on the saline lever. Only 1.0 mg/kg of methamphetamine exerted cues which resembled those of *d*-amphetamine; i.e., 91% of the lever presses occurred on the *d*-amphetamine lever following this drug.

Effects of AMPT on the d-Amphetamine-Saline Discrimination. The re-determination of the dose response curve for *d*-amphetamine produced results almost identical to the first determination, therefore these data will not be presented (see Fig. 2). In each case, 0.50 mg/kg of *d*-amphetamine produced around 76% responding on the *d*-amphetamine lever. After 200 mg/kg of AMPT, however, 0.50 mg/kg of *d*-amphetamine

Table 1. Per cent responding on *d*-amphetamine lever following various test drugs (Experiment IV)

Drug	Dose (mg/kg)	*N*	Per Cent
d-Amphetamine	1.0	6	91.3[a]
Psilocybin	1.0	6	23.6[b]
	0.5	6	27.2[b]
Δ^9-THC	1.0	6	2.0[b]
	0.5	6	3.4[b]
Mescaline	10.0	6	0.0[b]
	5.0	6	11.2[b]
LSD-25	0.08	6	22.3[b]
	0.04	6	32.7[b]
Caffeine	20.0	6	55.1[b]
	6.0	6	1.0[b]
Methamphetamine	1.0	5	90.9[a]
Saline		6	13.6[b]

[a] Probability of *d*-amphetamine response being different from saline response due to chance; $P < 0.001$, χ^2 test.

[b] Probability of test drug choice response being different from *d*-amphetamine response due to chance; $P < 0.001$, χ^2 test.

produced only 40% responding on the *d*-amphetamine lever. ND responding was not disrupted.

Discussion

The results of the present study indicate that *d*-amphetamine can acquire strong control over differential lever responding. Accuracy gradually increased to around 90% during the first 40 days of training. Overton (1973) reports that amphetamines maintain only moderate control over differential responding because of the many training sessions (more than 20) required for differential responding to reach 80% correct. Schechter and Rosecrans (1973), however, trained rats to escape shock in a three compartment box, using 4.0 mg/kg of *d*-amphetamine and saline as the discriminative stimuli, and reported 80% correct responding in 10 sessions. In the present study, rats were responding better than 80% correct by Days 20—25 and, after 40 sessions, their accuracy increased to approximately 90%. Fewer trials to criterion are usually seen using shock-escape for two reasons. First, larger doses can be used because behaviorally toxic effects of larger doses are more effectively overcome by shock-motivated tasks than by food or water reinforced (lever choice) tasks and secondly, larger doses produce stronger discriminability. The present results are consistent with similar procedures also reporting

control over differential responding using *d*-amphetamine as well as other drugs as discriminative stimuli (Cameron and Appel, 1973; Harris and Balster, 1971).

This procedure seems quite sensitive to drug effects since even a very small dose (0.0625 mg/kg) produced *some* *d*-amphetamine-like responding (22% on the D lever *vs.* 11% after saline). The discriminable ED_{50} was estimated as 0.23 mg/kg. However, Waters *et al.* (1972) found the ED_{50} for *d,l*-amphetamine to be 0.15 mg/kg in a group trained to discriminate 0.3 mg/kg *d,l*-amphetamine from saline and the ED_{50} for a group trained to discriminate 2.5 mg/kg of *d,l*-amphetamine from saline was approximately 1.0 mg/kg. Thus, as Overton (1974) points out, the shape of the drug generalization gradient, and the ED_{50} as well, are largely determined by the training dose used.

In the third phase of the experiment the discriminative effects of 1.0 mg/kg of *d*-amphetamine were found to persist between 60 to 90 min. Delays longer than 90 min resulted in random lever choice (53% on D lever) and eventual responding primarily on the ND lever. The peak effect occurred 30 min post-injection, which was in fact the regular latency employed after all training and test drug injections. An attempt was also made to measure the onset of discriminable effects by testing the subjects immediately after D injection. Since, in each case, the rats' initial responses were on the D lever, other intervals between 0—30 min were not tested. Similarly, temporally-related stimulus properties have been shown for Δ^9-THC (Ferraro *et al.*, 1974) and nicotine (Schechter and Rosecrans, 1971; Hirschhorn and Rosecrans, 1973). Furthermore, the duration of the behavioral effects also appears to be a task-related parameter. Schechter and Rosecrans (1971) tested the duration of effects of 0.40 mg/kg nicotine and found that the stimulus properties of the drug lasted 20 min using shock escape and up to 80 min on a lever choice procedure. That the effects of *d*-amphetamine were detected almost immediately after injection is surprising because if the "offset" of a drug effect (discriminability) is a gradual process, the "onset" should be gradual as well. This point should be investigated more systematically.

Since the D and ND states continued to produce consistent, reliable discriminative effects, it was decided to administer various novel drugs to determine whether or not their discriminative properties are similar to those of *d*-amphetamine. In general, it has been reported that animals make D related responses during test trials with drugs similar to the training drug, but not when tested with dissimilar drugs (Overton, 1966). Thus, drugs can be classified according to their discriminable effects (Barry, 1974). The results of the present experiment, as well as others, indicate that the discriminable stimulus properties associated with amphetamine are highly specific. The only drug which produced

d-amphetamine-like responding was methamphetamine. The largest dose of caffeine tested produced random choice responding and larger doses were not given to avoid the disruptive effects of the drug on responding. *L*-amphetamine also elicits *d*-amphetamine-like responding (Schechter and Rosecrans, 1973) and only *d*-amphetamine, methylphenidate (Harris and Blaster, 1971) and dexedrine (Harris and Balster, 1970) transfer to the *d,l*-amphetamine state.

Rats trained to discriminate either *d*- or *l*-amphetamine from saline respond on the saline-related lever when tested with hydroxyamphetamine, a drug which is devoid of central activity but mimics the peripheral effects of amphetamine (Jones *et al.*, 1974). Thus the amphetamine "state" is related to stimulation of central and not peripheral amine receptors. Antagonism of the *d*-amphetamine cue by AMPT on the present task as well as on a shock escape task (Rosecrans *et al.*, 1973) implicates the catecholamines specifically on the mediating amine system with respect to the discriminative effects of *d*-amphetamine. AMPT also antagonizes a nicotine discriminative cue (Schechter and Rosecrans, 1972b) and since the nicotine and amphetamine cues are dissimilar (Schechter and Rosecrans, 1972b; Morrison and Stephenson, 1969), the amphetamine effects may be mediated along dopaminergic pathways as Schechter and Rosecrans (1973) point out.

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