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Effects of training dose on amphetamine drug discrimination: Dose–response functions and generalization to cocaine

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Abstract

Rats were trained to discriminate one of three doses of amphetamine (AM), 0.5, 1, or 2 mg/kg, from vehicle (VEH) in a two-lever, food-reinforced, drug-discrimination task. The purpose of the study was to investigate the nature of the shift of the dose–response curve and generalization to cocaine (COC) as a function of training dose. In order to preclude potential differences among the groups in stimulus control, the three training-dose groups were required to perform the discrimination at high and equivalent levels of accuracy. The shift of the dose–response functions to the right as a function of increasing training dose was not parallel. The slope decreased as training dose increased. There was a dose-dependent increase in AM lever responding to test doses of COC that tended to be affected by training dose. The results suggest that proper evaluation of training-dose effects requires that groups be trained to equivalent levels of stimulus control.

Keywords: Drug discrimination; Amphetamine; Cocaine; Training dose

1. Introduction

The drug-discrimination task has been used to investigate internal cue states in humans and other animals following administration of drugs (Kamien et al., 1993). By establishing a discrimination between a cue state induced by a training drug and the cue state present after administration of saline or vehicle (VEH), one can study the degree to which other drugs produce cue states similar to the training drug-induced cue, as well as the degree to which other drugs might block the training drug-induced cue. While the results of such generalization and blocking tests provide important information about the neural systems that underlie drug-induced cues, general drug-discrimination procedures are also useful in investigations of tolerance (e.g., Wood et al., 1984; Young et al., 1992), withdrawal (e.g., Emmett-Oglesby and Rowen, 1991; France and Woods, 1990), and abuse liability (e.g., Brady, 1991; Holtzman, 1990; Stolerman, 1992).

In all drug-discrimination studies, qualitative and quantitative aspects of the training drug cue are a function of a number of variables, including the specific drug, the specific dose, the route of administration, and the time since administration. The role of training dose on generalization has been studied with many drugs, including ethanol (e.g., Grant et al., 1997), LSD (e.g., White and Appel, 1982), nicotine (e.g., Perkins et al., 1996), cocaine (COC, e.g., Schechter, 1997), and phencyclidine (e.g., Beardsley et al., 1987). Nearly one-third of all such studies, however, used opioids as the training drug (e.g., Colpaert et al., 1980a,b; Holtzman, 1997; Picker et al., 1996; Shannon and Holtzman, 1979). From a review of studies with opioids, Comer et al. (1991) suggested that (a) as training dose increases, the dose–response function shifts to the right, and (b) generalization of the training-drug cue to novel cue states is also influenced by training dose. Both quantitative and qualitative characteristics of the training cue may change across different training doses, thus affecting the degree of overlap between the cue induced by the training drug and the cue induced by a given test drug. For example, Colpaert et al. (1980b) have reported that, as the training dose of fentanyl was lowered, fentanyl-appropriate lever responding increased following both opioid and nonopioid drugs.

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Our interest in studying the nature of amphetamine (AM)-induced cue states as a function of temporal parameters (e.g., Barrett et al., 1992; Caul et al., 1996) and repeated drug administration (e.g., Caul et al., 1997; Stadler et al., 1999) led to the question of whether the general conclusions regarding training dose from the opioid discrimination experiments apply to discriminations with AM as the training drug. To date, however, there are only four studies with AM that have evaluated the effect of training dose (Barrett and Steranka, 1983; Kollins and Rush, 1999; Rosen et al., 1986; Stolerman and D'Mello, 1981).

Stolerman and D'Mello (1981) trained three groups of rats to discriminate either 0.4, 1.0, or 1.6 mg/kg AM from VEH and investigated the degree of generalization to other CNS stimulants. Consistent with the research using opiates, Stolerman and D'Mello observed that the dose–response curves tended to shift to the right for the groups trained on the high relative to the low training-dose group. Furthermore, generalization of the AM training cue to COC, apomorphine, and *p*-hydroxyamphetamine was also affected by training dose. AM lever responding following COC and *p*-hydroxyamphetamine increased as training dose decreased, but AM lever responding following apomorphine decreased. Two aspects of the study, however, make interpretation of the results problematical. First, although three training doses were used, the results suggest that the 1.0- and 1.6-mg/kg groups were equivalent in that their dose–response curves overlapped and the ED_{50} values for AM and COC did not differ. Second, as the authors noted, discrimination performance for the low-training-dose group was considerably lower ($\sim$80% correct) than for the two higher-training-dose groups ($\sim$99% correct). This difference in stimulus control across groups may well have contributed to differences in slope and shape of dose–response curves and in generalization profiles. Since the Stolerman and D'Mello paper, only three studies have been conducted that evaluate the AM training cue as a function of training dose (Barrett and Steranka, 1983; Kollins and Rush, 1999; Rosen et al., 1986). Although the primary purpose of two of these studies (Barrett and Steranka, 1983; Rosen et al., 1986) was not to evaluate the effect of training dose, the data presented are relevant to this issue.

Rosen et al. (1986) used an AM vs. saline drug discrimination to study the effects of lead exposure. The behavior of their control group that was not exposed to lead is of interest here. Animals were trained to discriminate 1.0 mg/kg AM from saline. Dose–response functions and generalization to apomorphine and methylphenidate were determined. Both apomorphine and methylphenidate generalized to the AM cue. The training dose was then systematically lowered for each animal until the animal reached the lowest dose capable of supporting discrimination performance of at least 80% correct. Dose–response functions and generalization to apomorphine and methylphenidate were then redetermined. Consistent with the results of Stolerman and D'Mello (1981), lowering the training dose resulted in a leftward shift of the AM dose–response function. In contrast to Stolerman and D'Mello's results, lowering the training dose did not alter either the methylphenidate or apomorphine generalization profiles. This finding should be viewed with caution, however, because it represents the behavior of only four animals, each of which had a unique behavioral training and testing history.

Barrett and Steranka (1983), in a study designed to test the opponent process theory of motivation, investigated the extent to which chronic haloperidol treatment would induce an AM-like withdrawal cue. Withdrawal from chronic haloperidol was evaluated in two groups of animals trained to discriminate either 0.5 or 1.5 mg/kg AM from saline. The dose–response curve for the 1.5-mg/kg training-dose group was shifted to the right relative to that of the 0.5-mg/kg training-dose group. Linear regression equations computed on the two functions indicated the slopes did not differ as a function of training dose. During a nondrug test after chronic haloperidol treatment, evidence for an AM-like rebound cue was confirmed when both groups made significantly more responses on the AM lever than observed when the groups were tested on saline tests prior to chronic drug treatment. Also of interest was the finding that the group tested on the low dose made significantly more responses on the AM lever (44%) than the high-training-dose group (23%). However, as in the Stolerman and D'Mello study cited above, the training-dose groups were not trained to equivalent levels of discrimination. The 0.5-mg/kg training-dose group had a lower asymptotic level of discrimination (83% correct) than did the 1.5-mg/kg training-dose group (96%). This difference makes it difficult to independently evaluate the effect of training dose on the slope of the resulting dose–response functions.

Recently, Kollins and Rush (1999) studied the effects of training dose on the relationship between the discriminative stimulus and subjective effects of AM in humans. Separate groups of people were trained to discriminate either 10 or 20 mg AM from placebo. They were then tested with a range of drug doses and asked to estimate how much drug they received and rate the subjective effects produced. Consistent with the results of studies with rats, the dose–response function for the high training-dose group was shifted to the right relative to that for the low training-dose group. In addition, the subject-reported ratings of subjective effects of "improved performance," "like the drug," "stimulated," and "feel like talking or socializing" were also shifted to the right relative to those of the low-dose group. Subject-reported ratings of "anxious/nervous," "bad effects," "feel the drug," and "good effects" were not affected by training dose. Unfortunately, in this study, generalization tests with other drugs were not conducted, leaving the relationship between training dose and generalization of AM to other drugs undetermined in humans.

The purpose of the present experiment was to determine the effect of training dose (0.5, 1.0, 2.0 mg/kg) of AM on:

(a) the relative position along the dose axis of the AM dose–response functions determined for each of the three training-dose groups, (b) the slope of the three resulting dose–response functions, and (c) the extent to which training dose influences generalization of a novel drug to AM. In the present experiment, COC was used as the novel drug because the COC cue is similar but not identical to the AM cue (Stolerman and D'Mello, 1981; Goudie and Reid, 1988). Finally, in the present experiment, an important criterion was that the three training-dose groups were trained to high and equal levels of discrimination.

2. Method

The procedures used in this experiment were approved by the Institutional Animal Care and Use Committee of Vanderbilt University.

2.1. Subjects

Forty-eight male Sprague–Dawley rats were purchased from Harlan Sprague Dawley, Indianapolis, IN, at 80–85 days of age, and were maintained on a 12:12-h light/dark cycle (06:30–18:30 h light). Rats were individually housed and were given free access to food and water upon arrival. After 14 days, rats were placed on a food deprivation schedule to reduce their weight to 85% free-feeding weight. In order to maintain target weights throughout experimentation, the food pellets earned by the animals were supplemented with powdered food immediately following training or test sessions. Deprivation target weights were adjusted periodically to account for growth.

2.2. Apparatus

Six operant boxes, each housed in a sound-attenuating chamber, were used. The front panel of each box was divided into thirds by two clear plastic dividers that extended from the ceiling to the grid floor and protruded 6.0 cm into the chambers. Two of the three divisions were equipped with a response lever. Food reinforcement (45-mg pellets, P.J. Noyes) was delivered via a food hopper mounted on the opposite back panel. The house light in each box was illuminated at the beginning of each session and turned off when the session ended. Sessions were controlled and data recorded by a computer and interface equipment located in an adjacent room.

2.3. Drugs

The drugs used were D-amphetamine sulfate (AM) and cocaine hydrochloride (COC). AM and COC were dissolved in distilled water VEH and were administered in 1 ml/kg volume. The doses of D-AM and COC refer to the salt.

2.4. Preliminary training

Daily 20-min training sessions began 8 days after the onset of food deprivation. Shaping sessions without drug injection provided reinforcement for responses on the lever that eventually became the VEH-appropriate lever. Responding was reinforced on a continuous schedule of reinforcement (CRF) until 100 reinforcements were earned in a single session. Subsequent sessions included a subcutaneous injection of VEH 20 min prior to being placed in the operant chamber and a change of reinforcement schedule to variable interval 10 s (VI-10 s). After all animals made 100 responses on the VEH lever in a single session under these conditions, they were randomly assigned to one of three training-dose groups: 0.5, 1.0, or 2.0 mg/kg AM. These procedures were then repeated to establish responding on the AM-appropriate lever. The appropriate training dose of AM was administered subcutaneously 20 min prior to each session.

2.5. Discrimination training

Once shaping was completed, discrimination training began. Discrimination training was grouped into blocks of six sessions, each of which included three sessions with AM and three with VEH run in alternation, one session per day. As a precaution against the possibility that any effects of an AM training dose would be present during the next training session, at least one day-off followed every AM training day. Twenty minutes prior to each 20-min training session, animals were injected with AM (0.5, 1.0, or 2.0 mg/kg) or VEH. During the fifth and sixth sessions of each block, responses during the first 2.5 min were nonreinforced to allow assessment of discrimination performance unconfounded by reinforcement. Correct responses were then reinforced during the remaining 17.5 min of these sessions. The drug-appropriate levers were counterbalanced within and across squads in order to ensure that odor cues were not predictive of the correct lever. During training, the reinforcement schedule was changed from VI-10 s to VI-20 s. Also, in order to facilitate discrimination, a time-out (TO) for incorrect responding was introduced. Incorrect responses initiated the TO during which reinforcement was withheld for responses on the correct lever. Correct responses were reinforced again if no further incorrect responses occurred during the TO interval. The TO was set at 5 s initially and then increased to a final value of 10 s. Discrimination training was continued until all groups of animals made at least 85% of responses on the correct lever for both the AM and VEH conditions.

2.6. Dose–response assessment

After animals reached this discrimination criterion, a dose–response function was determined. Choice behavior was evaluated during 5-min nonreinforced test sessions for the training dose of AM for each group (0.5, 1.0, 2.0 mg/kg),

VEH, and six doses of AM other than the training dose (ranging from 0.125 to 1.0 mg/kg). Animals were injected with these doses 20 min prior to the test. Five doses (0.125, 0.25, 0.375, 0.5, and 0.75 mg/kg AM) were tested in all groups of animals. All animals within a training-dose group were tested at all doses. Between dose–response tests, animals received four retraining sessions, two with the training dose of AM and two with VEH. The last AM and VEH retraining sessions included the 2.5-min nonreinforced period in order to make sure that discrimination performance was being maintained above the 85% correct criterion level.

2.7. Generalization to COC

Following the completion of dose–response assessment, animals were given four retraining sessions as described above. Three doses of COC (2.5, 5, and 10 mg/kg) were tested. These doses were chosen based on the expectation that they covered the range that would produce little, moderate, and almost complete responding on the AM lever under the conditions of the present experiment (Colpaert et al., 1978; D'Mello and Stolerman, 1977; Huang and Ho, 1974; Huang and Wilson, 1986; Stolerman and D'Mello, 1981; Woolverton and Cervo, 1986). All animals were tested with all three doses of COC in a randomly determined order. Animals were injected intraperitoneally with COC 20 min prior to a 5-min nonreinforced test session. Between generalization tests, one retraining session with the training dose of AM and one with VEH were run to assess levels of discrimination.

2.8. Data analyses

Data are presented in terms of percent responses on the AM-appropriate lever, i.e., choice, made during the 2.5-min nonreinforced portion of training and retraining sessions, and during the 5-min nonreinforced test sessions. For all sessions, an animal's choice data were included in the analyses only if at least five responses were made. Statistical analyses were conducted using the BMDP statistical package. Within- and between-subject factors were evaluated using one- and two-way ANOVAs.

The log-linear regression equation for each animal was calculated using data from doses that produced AM lever responding between 15% and 85% for that animal's group. Mean slope and ED_{50} values were determined for each group and analyzed using between-subject one-way ANOVAs. Pairwise comparisons were evaluated using the Dunnett post hoc test.

3. Results

3.1. Discrimination training and retraining performance

Discrimination training was conducted over five blocks of six sessions each. During the nonreinforced period of the final training session with AM, correct responding was 92%, 90%, and 90% for groups 0.5, 1.0, and 2.0 mg AM, respectively. During the final training session with VEH, correct responding was 88%, 88%, and 91% for groups 0.5, 1.0, and 2.0 mg AM, respectively. The data from retraining sessions given between tests confirmed that all groups maintained discrimination performance above the criterion of 85% correct throughout the entire experiment.

3.2. Dose–response assessment

Fig. 1A shows responding across all doses tested, including the training drug conditions. Dose-dependent increases in responding on the AM lever were observed as the dose of AM was increased from VEH to the training dose [0.5-mg AM dose effect: $F(7,105) = 59.20$, $P < .001$; 1.0-mg AM dose effect: $F(7,105) = 70.37$, $P < .001$; 2.0-mg AM dose effect: $F(7,98) = 53.27$, $P < .001$]. Fig. 1B shows the log-linear regression functions for the three training-dose groups calculated on the basis of responding to only those doses that produced between 15% and 85% AM lever

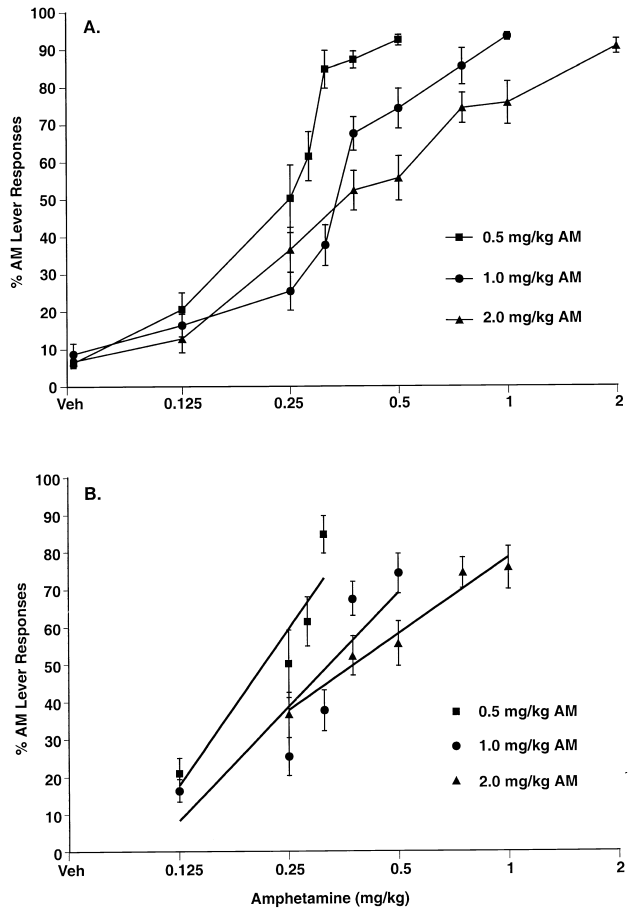

Fig. 1. (A) Dose–response functions for the three training dose groups. (B) Log-linear regression functions for the three training dose groups using data from test doses that elicited 15–85% AM lever responding. Error bars represent ±S.E.M.

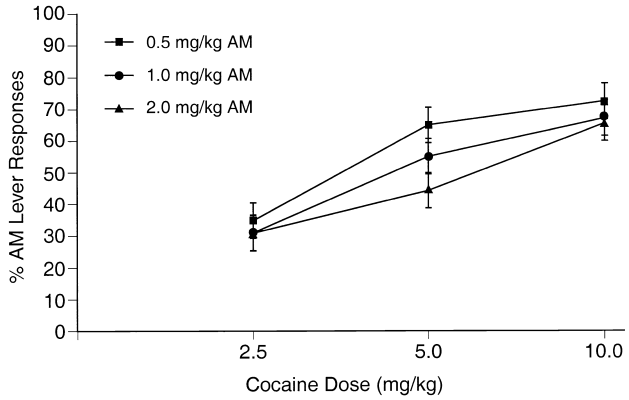

Fig. 2. Percent AM lever responding as a function of COC test dose for the three training dose groups. Error bars represent ±S.E.M.

responding. The slopes of the functions for the 0.5-, 1.0-, and 2.0-mg AM training-dose groups were 312.8, 172.7, and 51.7, respectively. As is apparent in Fig. 1B, the dose–response curves did not shift to the right in parallel fashion as a function of training dose. There was a significant difference among the slopes of the three groups, $F(2,45) = 58.72$, $P < .001$. Pairwise comparisons using Dunnett's test indicated that each group's slope differed from the slope of the other groups [0.5 vs. 1.0 mg/kg: $qC = 140.0$, $P < .05$; 1.0 vs. 2.0 mg/kg: $qC = 121.1$, $P < .05$; 0.5 vs. 2.0 mg/kg: $qC = 261.1$, $P < .05$). The ED_{50} values for the 0.5-, 1.0-, and 2.0-mg AM training-dose groups were 0.227, 0.359, and 0.548 mg/kg, respectively. These values were not significantly different from each other, $F(2,45) = 1.148$, $P = .327$.

3.3. Generalization to COC

The percent AM lever responding following administration of three doses of COC is shown in Fig. 2. As can be seen, a dose-dependent increase in AM lever responding occurred as the dose of COC was increased from 2.5 to 10 mg/kg [dose main effect: $F(2,132) = 17.89$, $P < .001$]. There was not a significant effect of training-dose group [$F(2,132) = 1.52$, $P = .22$] nor was there a significant Dose × Group interaction [$F(4,132) < 1$].

4. Discussion

The purpose of the present experiment was to determine the effect of AM training dose on three parameters: (1) relative position of the dose–response functions along the dose axis, (2) the slope of the dose–response functions, and (3) generalization of a novel drug to AM. Because the slope of dose–response functions is influenced by the asymptotic level of acquisition (Colpaert et al., 1980b; Comer et al., 1991), it was important in the present experiment that all three groups learned the discrimination at high and equivalent levels. As can be seen in Fig. 1A, all three training dose groups responded above 90% on the AM lever when given the training dose of AM, and above 91% on the VEH lever when given VEH.

As can be seen in Fig. 1A, five doses of AM intermediate to VEH and the 0.5-mg AM training dose, and six intermediate doses for each of the other groups, were tested. In order to evaluate the linear portion of these curves, only data from test doses that yielded AM lever responding between 15% and 85% were included in calculations of the log-linear regression equations plotted in Fig. 1B. This criterion was chosen to minimize the influence of floor and ceiling effects and maintain a range large enough to capture the dose–response relationship. The results from four intermediate doses for the group trained on 0.5 mg/kg AM and five doses for the groups trained on 1.0 and 2.0 mg/kg AM met this criterion. In agreement with results from previous training-dose studies, an increase in training dose was associated with a rightward shift of the dose–response function. It could be argued that the rightward shift of the dose–response function could, in part, reflect differential tolerance to the higher training doses that developed over the course of several months of training. This seems unlikely for several reasons. First, no loss of stimulus control was observed in any of the training dose groups throughout the duration of the experiment. Second, the results of studies designed to evaluate this issue have been reviewed by Young and Sannerud (1989) and support the conclusion that there is no evidence for the development of tolerance to the usual training doses in drug-discrimination studies. Third, in the present experiment, there was an interval of at least 48 h between consecutive doses of AM.

Results from the linear regression equations also indicated that the slopes of the dose–response functions decreased (Fig. 1B) as a function of an increase in training dose. The finding that slopes became flatter with increases in training dose is opposite to the conclusion previously reported for opioid studies (Colpaert et al., 1980a,b). However, in those studies, the effect of training dose on slope was confounded by the fact that asymptotic level of acquisition was not held constant across training dose groups. The effect of different levels of acquisition on slope of the dose–response function is evident in the Barrett and Steranka (1983) study where rats trained on 0.5 mg/kg AM made 83% of their responses on the AM lever at the conclusion of training compared to 96% for the group trained on 1.5 mg/kg AM. Although the slopes of the dose–response functions appeared not to differ between the two groups, because of the lower asymptotic level of acquisition, the slope of the dose–response function for the 0.5-mg/kg training dose group was flatter than it would have been if the group had reached the same 96% level of discrimination as reported for the 1.5-mg/kg group.

When animals were tested for generalization of the AM training cue to test doses of COC, AM lever responding increased as the dose of COC increased (Fig. 2). Although

the differences in responding among the training dose groups were not significant, the trend of the data, especially for the 5-mg/kg COC test, is consistent with the general view that increasing the training dose shifts the generalization curve to the right (Comer et al., 1991; Stolerman and D'Mello, 1981). In the present experiment, the percent AM lever responding to each test dose of COC was lower for the 2-mg/kg training dose group than for the 0.5-mg/kg group.

Finally, it is clear that the training dose chosen in drug-discrimination studies plays an important role in determining the dose–response function as well as the degree of generalization of the training cue to other compounds.

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