Pharmacology Biochemistry and Behavior, Vol. 56, No. 3, pp. 457–463, 1997

0091-3057/97 $17.00 + .00

PII S0091-3057(96)00301-2

Discriminative Characteristics of High and Low Cocaine Administration: Effect of Other Psychostimulants

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Received 28 December 1995; Accepted 30 April 1996

SCHECHTER, M. D. *Discriminative characteristics of high and low cocaine administration: Effect of other psychostimulants.* PHARMACOL BIOCHEM BEHAV **56**(3) 457–463, 1997.—Two groups of N/Nih male rats were trained to discriminate saline vehicle from either 2.0 mg/kg ($n = 10$) or 10.0 mg/kg ($n = 10$) cocaine in a food-motivated, two-lever operant paradigm. The rats trained at the low-dose cocaine took a significantly longer training period to reach criterion performance than did the high-dose cocaine group. In addition, the ED_{50} value for the 2.0 mg/kg cocaine-trained animals (0.465 mg/kg) was significantly lower than the ED_{50} value (2.105 mg/kg) for those animals trained at the 10.0 mg/kg dose of cocaine. This co-relationship of ED_{50} values for stimulus generalization decreasing with reduction in training dose was in contrast to the time-course of the two groups when tested from 15 to 240 min post-injection; this experimentation indicated that there was a non-significant difference in half-life for the 2.0 mg/kg ($t_{1/2}$: 97.1 min) vs. that of the 10.0 mg/kg cocaine-trained group ($t_{1/2}$: 83.4 min). Generalization tests with other purportedly dopaminergically-active drugs of abuse including 0.05–0.8 mg/kg *d*-amphetamine, 0.125–1.5 mg/kg methamphetamine and 0.125–1.0 mg/kg methcathinone indicated that the highest doses of each produced generalization and, with the exception of methcathinone, the ED_{50} values were significantly lower in the low-cocaine trained group. The stimulus properties of cocaine, as they generalize to amphetamine, methampetamine and methcathinone, can be explained by effects upon central dopaminergic neurons and may be qualitatively different in low- and high-dose trained rats. **Copyright © 1997 Elsevier Science Inc.**

Stimulus properties of drugs Cocaine Amphetamine Methamphetamine Methcathinone Dopamine Rats

THE STIMULUS properties of drugs have been widely used to characterize psychostimulants. Research has emphasized the discriminative stimulus properties of cocaine in an effort to determine this drug's mechanism(s) of action, in a continued search for possible psychotherapies to treat its addictive nature (2,8,23). In the great majority of these studies described in the cited reviews, the dose used to train rats to discriminate cocaine from its (saline) vehicle was 10.0 mg/kg administered intraperitoneally. In light of an earlier study (5) which sought the lower limits of discriminability of cocaine in cocaine-saline discrimination and, subsequently, suggested that 2.5 mg/kg cocaine was the ideal dose to be used to produce the maximum sensitivity, two recent studies (13,20) have used training doses of cocaine lower than 10.0 mg/kg. Both laboratories were the sites of experiments that trained rats to eventually discriminate either 2.0 (13) or 3.0 (20) mg/kg dose, slightly above the lowest dose ever successfully employed in this species, i.e. 1.25 mg/kg cocaine (9). One of these studies (20) discusses the discrepancies in published results between animals trained at the 10.0 mg/kg cocaine dose and those trained at lower doses. Unfortunately, this study, as well as the other recent publication (13), started by training rats with 10.0 mg/kg cocaine and then reduced the dose, in a subgroup of animals, to derive rats trained at the lower dose. Thus, neither study was able to directly compare the training rates of rats trained at 10.0 vs. 2.0 mg/kg cocaine since the same animals were trained, sequentially, at both cocaine doses.

The purpose of the present experimentation was to start, continue and finish training animals at 2.0 mg/kg vs. saline, as well as a second equal-numbered group of rats to the higher, and more generally used, 10.0 mg/kg cocaine dose. These animals were trained to criterion performance, whenever that was, in fact, reached and their learning rate was analyzed by application of a sessions-to-criterion measurement. Subse-

quently, the sensitivity to cocaine, as shown by dose-response experiments, as well as the time-course of the training dose effect in these animals, was tested. Lastly, the aforementioned studies and reviews have employed numerous and sundry classes of drugs to test if cocaine-appropriate responses generalize to these agents. It was the intent of this study to use the known psychostimulants: amphetamine, methamphetamine and methcathinone, as agonists to test for response generalization, in a dose-response manner, to indicate if there were differences in the sensitivity of high and low cocaine dose-trained rats when tested with other purportedly dopaminergically-active psychostimulants.

METHODS

Subjects

Twenty male rats employed in this study were of N/Nih descent and were obtained from the Small Animal Section of the National Center for Research Resources of the National Institutes of Health. Upon arrival, the rats were isolated for one week and subsequently placed into individual wire hanging cages in a facility with an ambient temperature of 20–22°C and maintained on a 12:12 light:dark cycle with lights on at 0600 h. Behavioral training/testing was conducted in a room separate from the animal colony. Tap water was offered continually in their home cages but daily rationing of approximately 16 g of a commercial rat chow allowed maintenance of their body weights at 85–90% of their free-feeding weights as determined by weighing an *ad libitum* control rat. This procedure was in place to facilitate motivation of operant performance for food reward. The twenty rats were randomly assigned to one of two equally numbered groups; one to be trained with 10.0 mg/kg cocaine hydrochloride and the remaining ten with 2.0 mg/kg cocaine hydrochloride.

Apparatus

Twelve standard rodent operant chambers (Lafayette Instruments Corp., Lafayette, IN) were used for training and testing. Having more chambers than rats in each group allowed for random daily assignment of rat to chamber. Each chamber was equipped with two operant levers and a food receptacle located at an equal distant between the levers. Solid-state equipment (Med Associates, St. Albans, VT) was located in an adjacent room and was used to control and record discrimination sessions.

Lever-Pressing and Discrimination Training

The food-deprived rats were trained to press one of the two levers under the drug condition and the second, identical, lever in the non-drug (saline vehicle) state. Training sessions were conducted once a day, five days a week, with one lever in each cage designated as the cocaine-lever and the second lever designated as the vehicle lever. To preclude any possible position preference, half of the rats of each group were required to press the cocaine lever located to the right of the food receptacle, whereas for the other five animals, the cocaine lever was to the left of the receptacle. The other lever was designated as the vehicle lever. Initially, all animals were trained to respond on the vehicle lever 15 min after the intraperitoneal (IP) administration of 1 ml/kg 0.9% NaCl in distilled water on a fixed ratio (FR) schedule of 1 [i.e., one response resulted in one (45-mg Noyes food pellet) reinforcer]. During ten consecutive training sessions, the FR schedule was gradually incremented to an FR10 in that 10 responses on the vehicle lever yielded one food reinforcer. The animal was removed from the operant chamber and returned to the home cage after receiving 40 reinforcers on each daily FR schedule.

Once an FR10 was established on these ten consecutive vehicle lever sessions, training began on the opposite lever (15 min) following the injection (IP) of an equal volume (1 ml/kg) of saline containing either 2.0 mg/ml cocaine or 10.0 mg/ml cocaine (n = 10 in each group). Rats, subsequently, were reinforced only for responding on the cocaine lever and, as with previous training after vehicle, the initial reinforcement schedule of FR1 was gradually incremented to FR10; this was accomplished over a period of six consecutive daily sessions.

The rats were considered to be trained to lever press after FR10 responding was established on both levers. Discrimination training was, subsequently, initiated 15 min after the daily administration of either the vehicle or cocaine. Animals received vehicle (V) or cocaine (C) according to a two-week, repeating, administration schedule: C,V,V, C,C; V,C,C,V,V. The first lever upon which 10 responses were accumulated at the beginning of each session was considered the selected lever for that daily session. At the time of the tenth response on either lever, presses on both the selected and nonselected levers were recorded. The session was continued, regardless of the correctness of the selected lever, until 400 responses were made on the correct lever for that session and, therefore, after 40 reinforcers (on the FR10 schedule) were received. The cocaine and vehicle training regimen continued for as long as necessary to allow all the animals to attain a criterion level of discriminative performance designated as correctly choosing the lever appropriate for the injection received (condition-imposed) in 8 of 10 consecutive daily training sessions, twice. The sessions-to-criterion (STC 1) measurement is indicative of the first session of 10 consecutive daily sessions in which 8 first-choice lever selections were initially made. The STC 2 relates to the first session of a second set of 8 of 10 correct consecutive lever selections. This 80% correct-lever selection performance level was required for a subject before dose-response testing was initiated.

Dose-response Generalization Tests

Of the 10 rats in the 2.0 mg/kg cocaine-vehicle training group, 7 animals were capable of reaching criterion performance within 12 weeks, whereas all of the 10 animals in the 10.0 mg/kg cocaine-vehicle group learned the discrimination. Thus, the former group is represented by an n = 7. Once the rats had reached the discriminative criterion, the discriminative training regimen was limited to every other day to maintain discrimination. On intervening days, rats were tested with doses of cocaine differing from their training dose in that the animals trained to 10.0 mg/kg cocaine were administered 5, 2.5 and 1.25 mg/kg cocaine on two occasions; one test following a vehicle maintenance session and one test following a training session at 10.0 mg/kg cocaine. In contrast, the animals trained at 2.0 mg/kg cocaine were administered higher doses of 10.0 and 5 mg/kg cocaine, as well as three lower doses of 1.0, 0.5, and 0.25 mg/kg cocaine. As before, each test followed both one vehicle maintenance session and one 2.0 mg/kg cocaine maintenance session. During all maintenance sessions, the animal's selected lever was determined for that daily session (the test component to be able to adjudge continued discrimination ability to trained drug dose) and this was followed by 40 reinforcers only if responses, on the FR10 reinforcement schedule, were made upon the state-correct lever (the training

component to allow for continued training to condition, drug or non-drug, imposed in training). The counterbalance procedure was used to control for any possible residual influences from the previous day's maintenance session. On those days that drug doses different from the training dose or novel drugs were tested, the animal was immediately removed from the chamber without receiving reinforcers upon accumulating 10 responses on either the cocaine- or vehicle-appropriate lever. This was done to avoid the possibility of reinforcement/ training in a condition/dose of cocaine that was not used in training. It was established ad hoc that, at any time during testing, if a rat's selected lever during maintenance discrimination sessions fell below the 80% criterion, i.e., less than 8 correct state-appropriate lever selections in 10 consecutive maintenance sessions, the data on that animal would be dropped from the results. This, however, did not occur in either of the two groups of animals.

Time-Course Testing

Once it was established that there was a dose-response relationship in regards to different doses than those used in training, the animals were administered the dose employed in their training in a series of experiments using different injection-to-testing intervals. These test-days were interspersed between maintenance cocaine and vehicle days so that each post-administration time-interval was tested once following the training dose of cocaine at 15 min and once following vehicle at 15 min post-administration. On test days, the animal was injected, (re)placed into their home cages for a selected period of time, removed and placed into the operant chamber and allowed to make 10 responses on either of the two levers. Once again, no food presentation (after 10 responses) was given to avoid reinforcement and possible training at times different than that used in training. The following post-injection intervals were used, on two test sessions each, in a random order: 30, 60, 120 and 240 min.

Generalization of Cocaine Responding to Other Psychostimulants

To assess the potential generalization (transfer) of the cocaine-cued response to *d*-amphetamine, methamphetamine and methcathinone, animals were tested with each novel drug/ dose in sessions interspersed with maintenance cocaine and vehicle sessions. Twenty min following administration of each of these drugs IP in doses of 0.05, 0.1, 0.2, 0.4, 0.8 mg/kg *d*-amphetamine, 0.125, 0.25, 0.5, 1.0 and 1.5 mg/kg methamphetamine and 0.125, 0.25, 0.5 and 1.0 mg/kg methcathinone, the animals were allowed to lever-press until ten responses were made on either of the two levers. At that time, they were immediately removed from the experimental chamber without receiving reinforcement. The first lever pressed 10 time was designated as the selected lever.

Measurements and Statistical Analysis

The percentage of rats selecting (accumulating 10 presses first upon) the designated cocaine-appropriate lever constituted the quantal discrimination measurement. The subjects were required to maintain a minimum of 80% cocaine-appropriate lever selections during drug maintenance sessions and were permitted a maximum of 20% cocaine-appropriate lever selections after vehicle injection for any 10 consecutive maintenance sessions. This established that an animal recognized the cocaine or vehicle stimulus cue at an 80% accuracy rate during maintenance and all animals met this criterion during the course of the entire study. Based on this maintenance criterion, it was determined ad hoc that, in generalization tests, a drug needed to produce lever-selection equal to, or greater than, 80% cocaine-appropriate responding to be considered to be able to substitute for (generalize to) the cocaine stimulus cue.

In addition to the quantal measurements, quantitative discriminative measurements were also calculated. The quantitative measurement is the number of responses on the cocaine lever divided by the sum of the responses on the cocaine and vehicle lever at the time that 10 responses are accumulated on either lever. This fraction is expressed as a percentage and, unlike the all-or-none quantal measurement, encompasses responses on both the selected and unselected levers; thus, it provides an assessment of the magnitude, as well as the direction of lever preference. A previous study (18) compared the quantal and quantitative indices directly and indicated that there was a perfect rank-order correlation between the ED_{50} values produced by each of the two methodologies. On the basis of those findings, with the results being in very close agreement, the quantal measurement was used throughout and was analyzed by using a computerized formulation (19) of the Litchfield-Wilcoxon (15) analysis that employs log-dose vs. probit measurements. This analysis permits ED_{50} values (with 95% confidence limits) for dose-response curves, as well as tests for parallelism between these curves and potency differences between drugs. The quantitative measurement was, nonetheless, employed to determine significant differences between learning rates of the two groups of rats with the 10.0 mg/kg cocaine vs. saline group representing an $n = 10$ and the 2.0 mg/kg cocaine vs. saline group, an $n = 7$ (Fig. 2).

Drugs

The training drug was cocaine hydrochloride with the 2.0 and 10.0 mg/kg dose calculated as the salt and dissolved in 0.9% sodium chloride solution made in distilled water. *D*-amphetamine sulfate, *d,l*-methamphetamine sulfate, as well as *d,l*-methcathinone hydrochloride, were administered in doses calculated as base and were injected in a constant volume of 1 ml/kg body weight in a 0.9% saline. All drugs were received from the Research Technology Branch at the National Institute on Drug Abuse (NIDA).

RESULTS

Using the bi-weekly, repeating administration schedule that commenced following establishment of the FR10 schedule of reinforcement on both levers (see METHODS), allowed for 5 cocaine and 5 vehicle administrations in a pseudo-random order. Thus, neither cocaine nor vehicle was administered on more than two consecutive days. The animals trained to 2.0 mg/kg cocaine vs. saline required a significantly greater number of training sessions to attain the STC 1 and 2 than did the rats trained to discriminate 10.0 mg/kg cocaine vs. saline (Fig. 1). In the higher training-dose group, the STC 1 and 2 (mean ± S.D.) was 11.6 (7.2) and 21.9 (7.1) sessions, respectively, whereas for the animals trained to 2.0 mg/kg cocaine, the STC 1 and 2 were 24.3 (11.2) and 40.8 (12.1) sessions, respectively. Both the mean (SD) STC 1 and 2 between 2.0 and 10.0 mg/kg animals were statistically different ($p < 0.05$; Student's unpaired, two-tailed, t test).

A second way to measure the learning curves of the two groups of animals is to use the quantitative measurements;

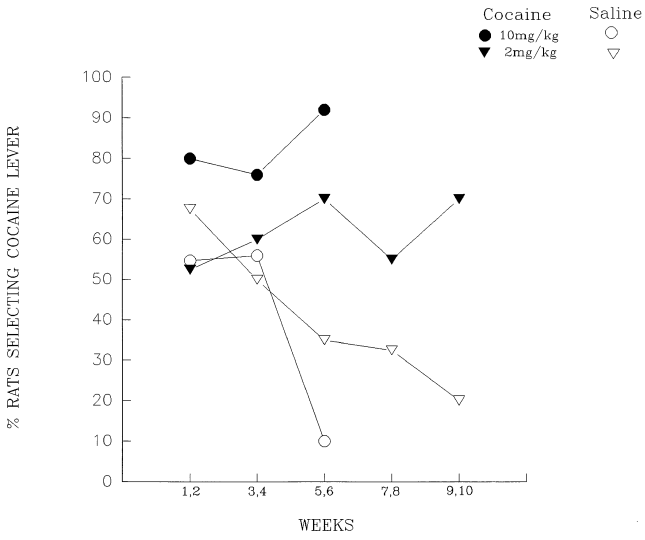

FIG. 1. Quantal measurement of learning curve of rats (n = 10/group) trained to discriminate saline from either 10.0 mg/kg cocaine or 2.0 mg/kg cocaine. Ordinate: Percent of rats selecting the cocaine-appropriate lever by accumulating 10 responses upon it before 10 responses were made on the saline vehicle-appropriate lever; Abscissa: Weeks of training with each two-weeks consisting of five cocaine (C) and five saline vehicle (V) sessions using the bi-weekly, repeating schedule: C,V,V,C,C; V,C,C,V,V. The 10.0 mg/kg cocaine-saline rats all learned the discrimination to criterion performance within six weeks. Of the ten rats trained to 2.0 mg/kg cocaine-saline, seven of ten rats learned the discrimination to criterion performance, yet all ten are represented in this figure through 50 trials (10 weeks).

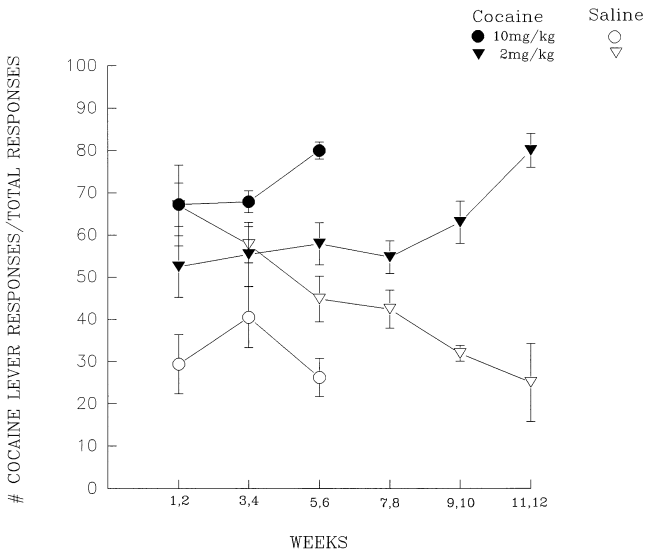

FIG. 2. Quantitative measurement of learning curve of rats trained to discriminate saline from either 10.0 mg/kg cocaine (n = 10) or 2.0 mg/kg cocaine (n = 7). Ordinate: mean (± S.D.) of 5 trials at each two weeks with high- and low-dose cocaine or saline vehicle presented as number of cocaine-lever responses divided by number of responses made on cocaine and saline lever, × 100 (see Measurement and Statistical Analysis section). Each point represents n = 10 for the high-dose cocaine animals and, in the case of the low-dose cocaine animals, only the 7 that eventually met criterion performance. Abscissa: weeks of training with each two-week period consisting of five cocaine and five saline vehicle sessions.

this is presented for the seven of the ten original rats in the 2.0 mg/kg cocaine vs. saline group who eventually learned the discrimination at criterion levels (Fig. 2). This figure is extended for an additional ten days of training beyond that seen with the quantal measurement (Fig. 1) and allows for standard deviations to be determined per condition over the two-week segments (5 sessions with cocaine and 5 sessions with saline). Non-parametric statistics were applied to these results and indicated significant differences (Student's t-test) in the quantitative measurements of the 2.0 mg/kg cocaine-trained animals learning the discriminative criterion which began in week 9–10 ($p < 0.05$) and continued into the last two weeks of training ($p < 0.01$). Thus, by using both quantal and quantitative measurements, the ten animals in the high-dose cocaine training group and the seven animals in the low-dose cocaine training group were adjudged to be able to differentiate the discriminative stimulus effects of these two doses of cocaine.

Not only was the rate of learning faster in the 10.0 mg/kg cocaine-trained animals, but the sensitivity to lower doses of cocaine was reduced as indicated by a higher ED_{50} value (Fig. 3). Thus, cocaine when trained at 10.0 mg/kg and tested at 5, 2.5 and 1.25 mg/kg cocaine generated an ED_{50} (95% confidence limits) value of 2.105 (1.444–3.069) mg/kg, whereas the rats trained to 2.0 mg/kg and tested with higher doses of 5 and 10.0 mg/kg cocaine, as well as lower doses of 1.25, 0.5 and 0.25 mg/kg cocaine, allowed the generation of an ED_{50} value of 0.465 (0.259–0.834) mg/kg; yielding a potency ratio of 2.185 and a significant ($p < 0.05$) difference from that derived for the higher cocaine-dose trained rats. Tests for parallelism (19) between these two lines indicated that their slopes were not significantly different within $p < 0.05$ probability; thus, they are parallel.

Administration of the training dose and testing at post-administration intervals longer than the 15 min used in training, produced a time-course relationship illustrated in Fig. 4. Calculation of the time that it took for each of the two doses to decrease from one point on the discrimination performance, i.e., percent cocaine-lever selected, to half that value was calculated to derive the half-life ($t_{1/2}$). It was found that the $t_{1/2}$ for animals trained at 2.0 mg/kg was 97.1 min in comparison to a $t_{1/2}$ equal to 83.4 min for the animals trained at 10.0 mg/kg. When analyzed by statistical methodologies (19), these findings were non-significantly different.The results of generalization tests in which other purported dopaminergically-active psychostimulants were tested for their ability to substitute for the 2.0 or 10.0 mg/kg cocaine-trained dose in each of the two groups of animals, are represented by the ED_{50} values in Table 1. The rats trained at the 10.0 mg/kg dose of cocaine had a significantly ($p < 0.05$) (19) higher ED_{50} after testing with various doses of cocaine, d-amphetamine and methamphetamine. This relationship did not occur with methcathinone. The slopes of the dose-response lines for each novel test drug were shown to all be parallel to each other and to that of the cocaine dose-response slopes.

DISCUSSION

Cocaine has been employed as a drug capable of controlling differential responding in a drug discrimination paradigm by numerous laboratories (2,8,23). In the great majority of these published studies, a training dose of 10.0 mg/kg cocaine was trained in either Sprague-Dawley (4,16,21), Wistar (5,6,13),

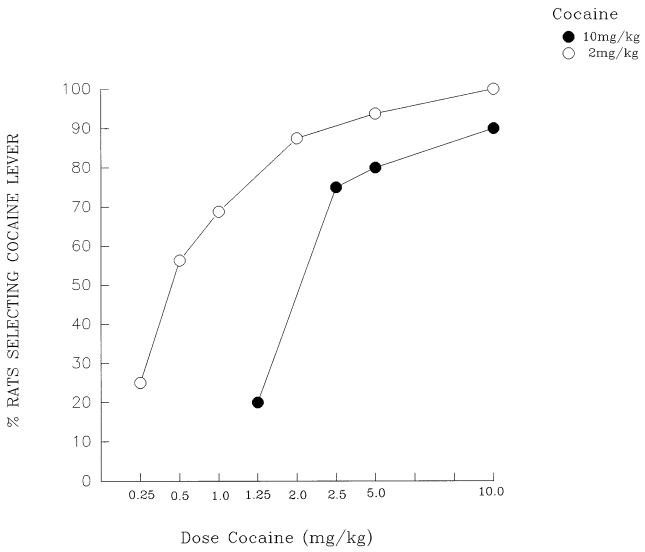

FIG. 3. Dose-response relationship in rats trained to discriminate between saline and 10.0 mg/kg cocaine ($n = 10$) or 2.0 mg/kg cocaine ($n = 7$). Ordinate: Percent of each group selecting the cocaine-appropriate lever after two trials at each dose. Abscissa: Dose cocaine, in mg/kg, tested in trials interspersed with maintenance saline and cocaine training dose sessions.

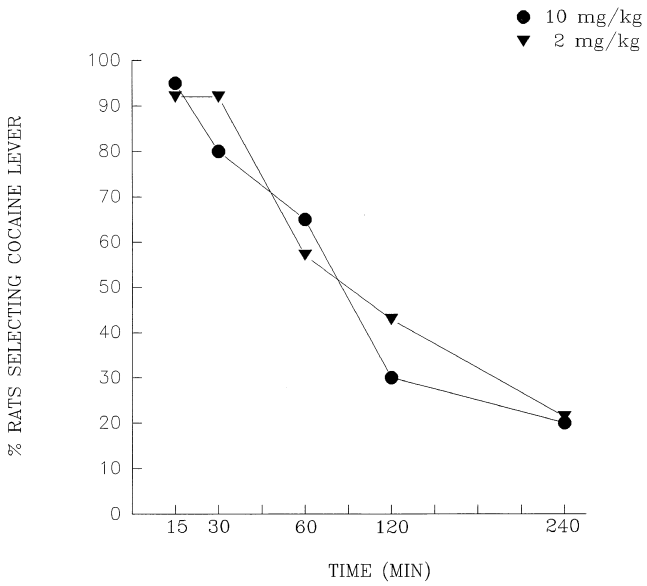

FIG. 4. Time-course relationship between rats trained to discriminate 10.0 mg/kg cocaine and 2.0 mg/kg cocaine vs. its vehicle. Ordinate: Percent of rats in each group selecting the cocaine-correct lever; Abscissa: Post-injection testing time in minutes with each post-injection period tested on two occasions.

Long-Evans (22) or hooded (18) rats. The present study employed a methodology, with only minor changes, that had been used as early as 1979 (6) to train rats to discriminate between cocaine and saline. In light of the large number of lines of rats used previously, the present study intended to use a heterogenously-derived breed of rat from the NIH (N/Nih rats), that were originally bred by intercrosses from eight lines of inbred rats to endeavor to ensure genetic heterogeneity. In this way, it was hoped that the possibility of differences between 2.0 and 10.0 mg/kg cocaine training doses could not be ascribed to the training of, for example, Sprague–Dawley (20) vs. Wister (13) rats. The advantage in using this line of rats has previously been discussed (11). In addition, the present work intended to expand upon two previous publications that trained animals to lower doses of cocaine by first training them to 10.0 mg/kg and, subsequently, reducing (fading) the training dose. The present study employed 2.0 mg/kg from the beginning of training in order to be able to compare learning rates, dose-response relationships and the generalization to other central nervous system stimulants. This last aim was to determine if differences in the training doses of cocaine could alter the generalization, albeit discriminability, of novel drugs when tested. This point was previously addressed using three different training doses (0.4, 1.0 and 1.6 mg/kg) of amphetamine and it was shown that rats trained to discriminate amphetamine generalize to the dopaminergically-active drug apomorphine only when trained with the highest dose of amphetamine (18).

In the continued training of those rats with 2.0 mg/kg cocaine as the training dose, it was seen to take a significantly longer time to reach criterion performance as defined by sessions-to-criterion (see METHODS; Figure 1 and 2). As previously shown (5), acquisition of the discriminative criterion takes longer with decreasing training dose and, as also shown in previous studies, animals trained with lower doses often are unable to reach criterion performance. Thus, as previously reported (9,20), the present study indicated that three of the ten rats assigned to be trained to 2.0 mg/kg cocaine never reached criterion performance. Although there was a significant difference in sessions-to-criterion between the 2.0 and 10.0 mg/kg cocaine-trained rats, the sessions-to-criterion of the high-dose group was similar to animals previously reported to be trained with 10.0 mg/kg (e.g., 22.6 sessions; 5). As stated, no previous study compared the training of rats from beginning-to-criterion performance with both 2.0 and 10.0 mg/kg cocaine. However, rats were trained to discriminate between a 10.0 and 56 mg/kg dose of caffeine in which the rats in the low dose training group required approximately twice as many sessions as those in the higher dose training group. In addition, the failure rate amongst rats at the low dose of caffeine suggested to the authors (17) that they were approaching the lower limits of caffeine discriminability and that the high and low dose of caffeine may be producing overlapping, but qualitatively different, discriminative stimuli along a continuum of dose. This, in effect, may be happening in the present study

TABLE 1

ED_{50} (95% CONFIDENCE LIMITS) VALUE OF DRUGS TESTED IN RATS TRAINED TO DISCRIMINATE BETWEEN SALINE AND 2.0 OR 10.0 mg/kg COCAINE

	Cocaine Training Dose (mg/kg)	
Drug	2.0	10.0
Cocaine	0.465 (0.259–0.834)	2.105 (1.444–3.069)*
d-Amphetamine	0.071 (0.043–0.119)	0.233 (0.166–0.325)*
Methcathinone	0.208 (0.136–0.316)	0.262 (0.161–0.425)
Methamphetamine	0.158 (0.099–0.254)	0.440 (0.310–0.625)*

*Significant difference ($p < 0.05$) from ED_{50} value determined for rats trained at 2.0 mg/kg cocaine.

using cocaine as the drug to control discriminative performance.

Not only did it take significantly longer to train the animals to 2.0 mg/kg cocaine than it did at the higher dose, the ED_{50} value for this low-dose group was significantly lower (Fig. 3). This co-relationship of ED_{50} for stimulus generalization decreasing with a reduction in training dose has been shown to be the case in many drug-discrimination experiments (7). This work suggests that the pharmacological selectivity of the training drug at different doses contributes to changes in potency and slopes of its own generalization gradient and to substitutions with novel test drugs.

Although the ratios of the drugs in this paradigm may, indeed, be co-determined by the training dose (16) with lower training doses producing lower ED_{50} values obtained during drug dose-response determination (18), there was no significant difference in the time-course of effect with both 2.0 and 10.0 mg/kg cocaine. Both groups of rats evidenced vehicle-like performance at 24 hr post-administration and the calculated half-life of 84–97 min postadministration was not significantly different (Fig. 4). In one of the only other studies in which the discriminative time-course of cocaine was measured after administration of 10.0 mg/kg cocaine, a calculated half-life of approximately 100 min (16) was derived.

The generalizability of cocaine-induced discriminative responding to other drugs, especially amphetamine and methyl-(or meth)amphetamine, has received much study as indicated by the reviews cited in the INTRODUCTION. All of these studies were done with the 10.0 mg/kg cocaine training dose and allowed for ED_{50} values ranging from 0.8 mg/kg (5) to 2.8 mg/kg (16). The present finding of an ED_{50} value of 2.105 mg/kg for the 10.0 mg/kg group is, therefore, within that reported range. Nevertheless, the 2.0 mg/kg training group showed a significantly ($p < 0.05$) lower ED_{50} value when tested with numerous doses of cocaine (Table 1). This would, once again, suggest that the results of drug discrimination experiments, especially to the extent of generalization to the trained compound and others tested, critically depends upon the training dose as recently stated in a review of the literature (1).

The same relationship also appeared to occur in generalization experiments when amphetamine and methamphetamine were tested in that there was a significantly higher ED_{50} value in animals trained at 10.0 mg/kg cocaine than there was for those trained at 2.0 mg/kg cocaine (Table 1). Many investigators have reported the ability of *d*-amphetamine to substitute in animals trained to discriminate 10.0 mg/kg cocaine (3). In actuality, dose-response relationships have allowed both cocaine and amphetamine ED_{50} values to be generated in the same animals and in some cases, cocaine appears more potent (cocaine ED_{50}: 0.14 mg/kg vs. amphetamine ED_{50}: 0.15 mg/kg)(6), whereas, in other studies, amphetamine seems more potent (cocaine ED_{50}: 2.2 vs. amphetamine ED_{50}: 0.38; 18; cocaine ED_{50}: 2.8 vs. amphetamine ED_{50}: 0.3)(16). In the present study, amphetamine, in both the high and low cocaine dose-trained animals, was shown to have a significantly ($p < 0.05$) lower ED_{50} value and, thus, amphetamine appears to be more potent in our experimentation. Based on previous drug discrimination studies, there is a possibility that cocaine and amphetamine share, as indicated by cross-generalization, certain interoceptive cueing properties but that, in fact, they may differ in some small way (18). This was most clearly shown by a definitive experiment which, after extensive training, showed that rats were capable of discriminating between amphetamine and cocaine in a 2-lever, drug vs. drug, discrimination task (10).

Similar to *d*-amphetamine, discriminative responding after administration of methamphetamine has been shown to generalize in animals trained to 10.0 mg/kg cocaine with an ED_{50} value roughly equivalent to that seen with amphetamine (ED_{50} for *d*-amphetamine: 0.17 vs. ED_{50} for methamphetamine: 0.15 mg/kg)(6). In the present study, the generalization to methamphetamine showed an even greater difference in ED_{50} values. The explanation for exactly why the generally more potent methamphetamine was shown to have a higher ED_{50} value than amphetamine in both the high- and low-dose trained animals remains to be determined, i.e., ED_{50} value for methamphetamine was approximately twice that of *d*-amphetamine. Lastly, the generalization of cocaine responding to the racemer form of cathinone has been shown to occur with cocaine approximately twice as potent as cathinone (12). In the present study, this relationship was true for the lower dose cocaine-trained animals but not in the higher-dose trained animals; the ED_{50} values were not significantly different for methcathinone between the two groups of animals. The most parsimonious explanation for this resides in the possibility that only functionally similar drugs act through similar neuromechanisms that have the effects to substitute for the training drug. There are, thus, similarities and dissimilarities in the cueing properties (e.g., as to the extent of dopamine release and/or reuptake inhibition) in each of the psychostimulants tested to suggest that methcathinone may be the most unique amongst the drugs employed. Nonetheless, as all novel drugs tested produced greater than 80% selection of the cocaine-appropriate lever in both 2.0 and 10.0 mg/kg cocaine-trained animals, and their dose-response effect slopes were parallel, there is every reason to believe that, at least, a major component of each of these drugs' ability to produce discrimination stimulus effects results from a common mechanism. Over the past decade, a plethora of results from various experimental techniques have been reported that suggest that it is the dopaminergic mesolimbocorticoid neurons that are critical in the behavioral effects of all psychostimulants. This allows positing of the dopamine hypothesis which defines the ability of cocaine to bind to the dopamine transporter and, thus, block its reuptake, as its primary mechanism of action (14). With this hypothesis evidenced, the behaviors associated with amphetamine, methamphetamine and methcathinone may be fitted into this model with the *proviso* that these other drugs lead to increased synaptic concentrations by what appears to be dopamine release rather than reuptake inhibition. Nonetheless, the ability of cocaine to affect other neurotransmitters, such as the serotonin reuptake transporter (3), must be considered as a possible defining difference between it and other psychostimulants. Further experimentation is suggested to evaluate the role of serotonin uptake inhibition in the discrimination of high vs. low doses of cocaine. The lower-dose cocaine discrimination, by virtue of increased sensitivity, may also be useful for the identification of other neurotransmitter mediation, such NMDA (13), in the cocaine-induced discriminative stimulus.

ACKNOWLEDGEMENTS

The author would like to sincerely thank Denise McBurney for her excellent technical assistance, as well as graphic expertise, Sheila Formick and Martha Hilgert for their continued and tenacious word processing skills, and Dr. John W. Boja for his insightful conversations throughout the course of this work.

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