Pharmacology Biochemistry & Behavior, Vol. 31, pp. 239–242. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

BRIEF COMMUNICATION

Advantages and Disadvantages of a Rapid Method to Train Drug Discrimination

MARTIN D. SCHECHTER

Department of Pharmacology, Northeastern Ohio Universities College of Medicine, Rootstown, OH 44272

Received 30 November 1988

SCHECHTER, M. D. *Advantages and disadvantages of a rapid method to train drug discrimination.* PHARMACOL BIOCHEM BEHAV **31**(1) 239–242, 1988.—In an effort to reduce the often extensive period of time needed to train rats to discriminate between a drugged and nondrugged state, a fast training regimen was employed with 1.5 mg/kg 3,4-methylenedioxymethamphetamine (MDMA) used as the training drug in ten rats. This protocol consisted of one to three training sessions per day and it was compared to the more conventional method of once-per-day training in an equal number of rats. Results indicate that the fast-trained rats learned the discrimination in significantly fewer sessions than the slowly-trained rats. However, the subsequent dose-response experiments indicate that when the fast-trained rats are tested with various doses of MDMA, without prior vehicle treatment, their sensitivity to the drug is less than that of the slowly-trained rats. When a vehicle session is presented prior to drug dose-response testing, both groups perform similarly. It appears that the preceding vehicle sessions function as a reference point for the fast-trained rats and, although the more rapid training regimen allows for faster learning, these treatment regimens should be employed with caution when subsequent dose-response tests and generalization tests with other drugs are conducted.

Drug discrimination MDMA Dose Response Training Rats

THE behavioral paradigm involving the discriminative properties of drugs has gained widespread acceptance as a research tool as attested to by over 600 publications (7,9). This technique has provided information concerning drugs of various and diversified pharmacologic classes and has been successfully used to generate abundant suggestive evidence regarding the mechanism of action of numerous psychoactive drugs (1,2). A major drawback of this behavioral paradigm is the extensive amount of time sometimes needed to train subjects to reliably discriminate between a drug and a nondrug state. The possibility of decreasing the amount of time needed to train rats in this procedure by employing an accelerated training regimen has recently been reported (3). It is not known, however, whether this procedure yields results similar to that obtained with the usual, slower procedure. It was the intent of the present study to compare the performance of rats trained to discriminate a centrally-active and abused drug 3,4-methylenedioxymethamphetamine (MDMA), by the more conventional, slower method with that of rats trained using this accelerated method.

METHOD

Subjects

Twenty male Sprague-Dawley (Zivic-Miller) rats weighing 225–275 g at the beginning of the experiment were individually housed with free access to water except during the experimental sessions. The rats were maintained at approximately 85% of their free-feeding weights by restricted feeding of a commerically-available rat chow and were trained 5 days per week.

Apparatus

Ten rat operant test cages (Lafayette Instrument Co., Lafayette, IN) were each equipped with two levers mounted 7 cm above a metal grid floor and 7 cm apart. Equidistant between the two levers and 2 cm above the floor was located a food pellet receptacle. The test cage was housed in a sound-attenuating cubicle equipped with an exhaust fan and a 9-watt house-light. Solid-state programming equipment (Med Associates, E. Fairfield, VT) was used to control and record each session and was located in an adjacent room.

Shaping to Lever-Press Procedure

The twenty food-deprived rats were administered vehicle (distilled water) intraperitoneally (IP) 20 min prior to the start of each of the first 10 shaping sessions of the experiment. They were then trained to press either the right (n=10) or left (n=10) lever to receive a food reinforcement (45 mg

Noyes pellet) under a fixed-ratio 1 (FR1) schedule. Shaping continued as the FR schedule was gradually increased to FR10 over a period of 6 days; this FR10 was maintained for 4 additional days. Before each of the subsequent shaping sessions, the rat received (IP) 1.5 mg/kg MDMA (provided by the N.I.D.A.) 20 min prior to the training session. The rats were then trained on an FR1 schedule on the opposite (the drug-correct) lever. The FR schedule was gradually increased over a 5-day period until an FR10 was obtained; this schedule was maintained for 4 additional days.

Discrimination Training

Once all animals were successfully shaped to press first one lever after vehicle administration and then the other lever after MDMA administration, the rats were randomly divided into 2 equal groups of 10 animals. For one group, the following 2-week, repeating schedule was used to train them to discriminate between MDMA (D) and its vehicle (V): V-D-D-V-V, D-V-V-D-D. The MDMA-appropriate lever for each animal remained constant throughout the experimentation and each injection condition (MDMA or vehicle) was administered once per day over a 5-day work week. This constitutes the discriminative training (postshaping) period for the traditionally- or slowly-trained rats.

The other group of 10 rats was trained according to the following repeating regimen with each day's schedule separated by a slash: VD/D/VD/VVD/VD/VD/VVD/D. Thus, each rat received from a minimum of one treatment a day to a maximum of three treatments a day; the drug treatment was always the last treatment in all days. This was planned so that there was no possibility of a drug aftereffect on the same day of training. After each treatment, the rats were allowed to receive 40 reinforcements after pressing the designated correct lever with 400 responses (on the FR10 schedule of reinforcement). On the multiple injection days, immediately following emission of those 400 responses, the animal was removed, injected with the second treatment (either vehicle or drug), replaced into its own cage for 20 min and then trained until 400 responses were again emitted on the appropriate lever.

The criterion for learning the discrimination in both groups was correct lever selection, as indicated by the first lever on which the rat completed the FR10 at the beginning of each session. Criterion performance was attained when each rat correctly selected the appropriate lever on 8 of 10 consecutive sessions, twice.

Dose-Response Testing

After all the rats had met the 8 out of 10 criterion twice, the animals received various doses of MDMA according to the following two-week schedule: D-DR_1-V-DR_2-D, DR_2-V-DR_1-D-DR_3, etc., where D=1.5 mg/kg MDMA, V=vehicle, DR_1=one other dose of MDMA, DR_2=another dose of MDMA. Thus, each dose was preceded by one session with vehicle and one session with 1.5 mg/kg MDMA. Any animal failing to maintain discrimination performance at the criterion level during these interspersed maintenance drug and vehicle sessions was eliminated from the study at that point. All doses were given IP 20 min prior to testing and each animal was allowed to lever press until 10 responses had been recorded on either lever. The rat was then immediately removed from the chamber, without receiving reinforcement, and was placed into its home-cage. This procedure precluded any continued training at a dose other than the training dose of 1.5 mg/kg MDMA. This constituted the unchallenged dose-response experimentation.

In addition, a vehicle-challenge dose-response relationship was conducted in which each of two groups was once again administered various doses of MDMA differing from the (1.5 mg/kg) training dose; but in this series of experiments they were administered and tested with vehicle immediately prior to the drug test dose. During these vehicle sessions, the animals were allowed to receive reinforcement on the vehicle-correct lever and after receiving 40 reinforcements, they were tested with a dose of MDMA and immediately removed upon pressing either lever 10 times.

Measurements and Statistics

The lever pressed 10 times first was designated the "selected" lever and the percentage of rats selecting the lever appropriate for MDMA was the quantal measurement of discrimination. The quantal data are presented as percent correct first choices on the MDMA lever. The number of lever presses on the MDMA-correct lever divided by the total number of responses on both levers prior to 10 responses times 100 constitutes the quantitative measurement. Mean (and standard deviation) of quantitative measurements were calculated across all rats on each day. Both measurements are reported as suggested previously (8). Quantal data were analyzed by the method of Litchfield and Wilcoxon (4) which employs probit vs. log-dose effects and allows for testing for parallelism and derivation of ED_{50}'s. Quantitative data were compared by a two-tailed paired t-test of means ($p<0.05$). In addition to these measurements, the sessions-to-criterion, which is defined (5) as the first session of the 8 out of 10 consecutive sessions in which the rat correctly chose the appropriate lever, was calculated for each of the two groups; sessions-to-criterion 1 (STC 1) being the first session of 10 consecutive sessions in which the animals responded correctly the first time and STC 2 indicating the first of the second consecutive training session in which 8 correct first choice responses were made in each of the two groups.

RESULTS

Sessions-to-Criterion

The slowly-trained animals required a mean (±standard deviation) of 7.8 (5.2) to attain the first 8 of 10 consecutive first-choice correct response, whereas the fast-trained MDMA group required a mean of 3.9 (2.8) sessions to achieve STC 1. This is significantly faster ($p<0.05$) than the slowly-trained rats. In addition, the slowly-trained rats required 20.4 (4.4) sessions to attain criterion performance again (STC 2), whereas the fast-trained group acquired this criterion in 15.4 (3.5) sessions; this difference is significant at a $p<0.01$ level.

Dose-Response Relationships: Unchallenged

The unchallenged dose-response relationship in the slowly-trained MDMA animals and the fast-trained MDMA animals appears in the second and fourth columns of Table 1. Decreasing doses of MDMA produced decreased discriminative responding in both groups of rats. The ED_{50} in the slowly-trained rats was 0.27 mg/kg for the quantal data and 0.30 mg/kg for the quantitative data. In the fast-trained MDMA animals, the ED_{50} generated from the three doses tested was 0.86 mg/kg for the quantal data and 0.84 mg/kg for

TABLE 1

DOSE-RESPONSE RELATIONSHIP TO MDMA IN SLOW- AND FAST-TRAINED RATS: EFFECT OF VEHICLE CHALLENGE PRIOR TO TESTING

Dose MDMA (mg/kg)	Slow-Trained						Fast-Trained					
	Unchallenged (10)*			Veh-Challenged (9)			Unchallenged (9)			Veh-Challenged (8)		
1.5	97.5	88.4	(5.1)	100.0	97.4	(3.8)	92.6	81.7	(11.8)	95.8	87.6	(10.6)
1.0	87.5	77.0	(6.4)	88.9	89.1	(15.5)	55.6	59.0	(7.2)	88.9	86.4	(11.5)
0.75		ND		55.6	54.6	(0.6)		ND			ND	
0.5	62.5	56.0	(13.3)	16.7	23.2	(6.4)	11.1	22.4	(1.1)	27.8	33.0	(16.5)
0.25	50.0	48.8	(7.8)		ND			ND			ND	
0.125	25.0	30.0	(2.2)		ND			ND			ND	
ED_{50} (mg/kg)	0.27	0.30		0.61	0.67		0.86	0.84		0.63	0.63	

ND: not determined.

*n=10 rats. Smaller n's resulted from rats being omitted from the results because of their failure to maintain criterion performance during dose-response trials.

the quantiative data. Analysis and comparison of the dose-response lines (4) indicated that they are parallel within 95% confidence limits (calculated $t=0.57 <$ critical $t=2.57$).

Dose-Response Relationships: Vehicle-Challenged

When vehicle was administered and tested immediately prior to drug dose-response testing in each of the two groups, the dose-response relationships are represented in the third and fifth columns of Table 1. In the slowly-trained animals, the vehicle-challenge produced an ED_{50} of 0.61 mg/kg for the quantal data and 0.67 mg/kg for the quantitative data. The challenge with vehicle also shifted the dose-response curve in the fast-trained MDMA animals with an ED_{50} of 0.63 for both the quantitative and quantal data. In both cases, these lines were parallel to each other.

DISCUSSION

The results of the present experiments indicate that employment of a training regimen that provides for more than one training session per day to train rats to discriminate a psychoactive drug, in this case MDMA, allows attainment of criterion performance faster than the more conventional training method, but at a later cost. Thus, as seen in the analysis of the session-to-criterion, the fast-trained group, who received drugs one or more times per day, had a significantly faster sessions-to-criterion 1 and sessions-to-criterion 2. They may, therefore, be adjudged to have learned to discriminate at a faster rate, not only in terms of days of training, but in terms of actual sessions needed. This result is in agreement with a recently published study employing cocaine or pentylenetetrazol as the training drug (3).

The caveat to the experimenter appeared later when dose-response relationships were tested. The ED_{50} (0.27 mg/kg) of the slowly-trained rats was considerably lower than the ED_{50} in the fast-trained MDMA group (0.86 mg/kg); this would suggest that the slowly-trained rats were more sensitive to the stimulus effects of MDMA. The fast-trained group was, in reality, trained not only to discriminate the effects of MDMA, but to discriminate them vs. a vehicle discrimination that was always given prior to drug training. Thus, the fast-trained MDMA animals had imposed upon them a reference point, i.e., the nondrug state, and that this immediately preceding nondrug reference point when not present, as in the unchallenged dose-reponse trials, allowed for a compromise in their sensitivity. When the slowly-trained MDMA animals were given a vehicle test/training session immediately prior to a drug dose-response session, their ability to discriminate lower doses of MDMA actually decreased, whereas the same treatment (in fact, the one that they were used to) in the fast-trained MDMA animals improved that group's sensitivity.

Another possible limitation to the widespread use of the accelerated training method resides in the pharmacokinetic properties of the drug used in training, as previously discussed (3). Thus, if a drug has a long half-life, the required five half-lives to allow clearance from the body may preclude its use on a daily basis. In the case of the present study, the calculated half-life of MDMA of 100 min (6) insured that the drug was adequately dissipated during the 24 hr between training sessions.

ACKNOWLEDGEMENTS

The author would like to thank Denise Lovano-McBurney for her continued excellence in laboratory experimentation and Drs. Michael W. Emmett-Oglesby and Donald Overton for their helpful and constructive comments. This work was supported entirely by NIDA grant No. 04181.

REFERENCES

1. Colpaert, F. C.; Rosecrans, J. A., eds. Stimulus properties of drugs: Ten years of progress. Amsterdam: Elsevier/North-Holland Biomedical Press; 1978.
2. Colpaert, F. C.; Slangen, J. L., eds. Drug discrimination: Applications in CNS pharmacology. Amsterdam: Elsevier Biomedical Press; 1982.
3. Harris, C. M.; Wood, D. M.; Lal, H.; Emmett-Oglesby, M. W. A method to shorten the training phase of drug discrimination. Psychopharmacology (Berlin) 93:435–436; 1987.
4. Litchfield, J. T.; Wilcoxon, F. A simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther. 96:99–106; 1949.

5. Overton, D. A. Comparison of the degree of discriminability of various drugs using the T-maze drug discrimination paradigm. Psychopharmacology (Berlin) 76:385–395; 1982.
6. Schechter, M. D. MDMA as a discriminative stimulus: Isomeric comparisons. Pharmacol. Biochem. Behav. 27:41–44; 1987.
7. Stolerman, I. P.; Baldy, R. E.; Shine, P. J. Drug discrimination: A bibliography. In: Colpaert, F. C.; Slangen, J. L., eds. Drug discrimination: Applications in CNS pharmacology. Amsterdam: Elsevier Biomedial Press; 1982:401–424.
8. Stolerman, I. P.; D'Mello, G. D. Role of training condition in discrimination of central nervous system stimulants. Psychopharmacology (Berlin) 73:295–303; 1981.
9. Stolerman, I. P.; Shine, P. J. Trends in drug discrimination research analyzed with a cross-indexed bibliography, 1982–1983. Psychopharmacology (Berlin) 86:1–11; 1985.