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D-AMPHETAMINE AS A DISCRIMINATIVE CUE: DRUGS WITH SIMILAR STIMULUS PROPERTIES *

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Rats were trained to choose between the side compartments of a 3-chambered shock-escape apparatus according to whether they were injected (i.p.) with 4.0 mg/kg d-amphetamine or 0.9% saline. The d-amphetamine drug state acquired all the properties of a discriminative stimulus by producing interoceptive cues. Doses of 0.4 mg/kg nicotine, 7.4–29.7 mg/kg mescaline, 4.0–8.0 mg/kg fenfluramine and 0.048 mg/kg LSD failed to produce an amphetamine-like cue. However, l-amphetamine, 8.0 mg/kg, produced responses shown to be statistically similar to the 4.0 mg/kg training dose of d-amphetamine.

d-Amphetamine
Nicotine
l-Amphetamine
State-dependent learning
LSD

1. Introduction

Drug conditions produced by centrally active drugs may be used in place of external discriminative stimuli, such as visual and auditory cues, to provide a basis for differential responding. The specific drug state acquires discriminative control of instrumental conditioning by producing interoceptive cueing. Furthermore, drugs with similar pharmacological actions are relatively indistinguishable from each other when equally effective doses are compared (Overton, 1971).

The facilitatory effect of d-amphetamine upon the acquisition of behavior in rats is well documented (Kelemen and Bovet, 1961; Doty and Doty, 1966; Latz et al., 1966; Orsingher and Fulginiti, 1971), but its use in a state-dependent drug context has been limited. Belleville (1964) reported that lever-pressing responses made, to obtain food reinforcement, by rats extinguished more slowly after amphetamine administration during acquisition, than if drug treatments were changed. Lal (1969) observed that amphetamine was capable of producing a 'behavior-controlling state' in mice trained on a conditioned avoidance response.

The purpose of this study was to train rats to discriminate between d-amphetamine and saline, in a 3-compartment shock-escape box, and to investigate the ability of various drugs to produce an amphetamine-like cue. Two problems of special significance in behavioral studies with amphetamine are the anorexic effects of the drug (Teitelbaum and Derks, 1958; Faidherbe et al., 1962; Poschel, 1963) and the development of tolerance to repeated administrations (Schuster and Zimmerman, 1961; Zimmerman and Schuster, 1962). To avoid possible effects of amphetamine on motivation to receive food reinforcement, the present study used a shock-escape technique for-

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merly employed by Stewart (1962) and, to avoid tolerance, amphetamine was administered at a maximum of 3 times in a 7-day week (range 1–3 times).

2. Materials and Methods

2.1. Subjects

10 experimentally-naive adult female albino rats weighing 200–250 g were purchased from Charles River Breeding Laboratories, Wilmington, Mass. They were housed individually with food and water ad libitum.

2.2. Apparatus

Rats were trained to escape from 0.5 to 0.6 mA scrambled shock in a 3-compartment box, previously described (Stewart, 1962; Schechter and Rosecrans, 1971a). Shock was applied to the grid floor upon the depression of a hand-key, and could be immediately discontinued upon release of the key. The center compartment, 26 X 26 cm, was provided with access to the two side compartments, each 12 X 26 cm, by an 8 cm X 8 cm opening cut in center of each separating partition. The side compartments were exactly alike and the front of the box was made of plexiglass to allow viewing.

2.3. Training

In order to minimize the possible systematic effects of position preference, the ten subjects were divided ramdomly into two equal groups. One group was required to enter the left compartment after d-amphetamine (4.0 mg/kg, i.p.) administration to escape the shock, whereas, the other group had to enter the right compartment after amphetamine administration. On each training session, a rat was injected with either amphetamine or saline. Ten minutes later it was dropped from a height of approximately 6 in, into the center compartment (with its head facing the back wall) with the shock already turned on and allowed to run freely until it reached the correct compartment; at which time the shock was instantaneously turned off by releasing a spring-loaded key. Each rat received 8 training trials per daily session; spaced 10–15 sec apart. The same choice of compartment (either right or left) was required on all trials during a given session. Rats received 1 session per day, 5 days per week.

For each rat, the 2 states, viz., amphetamine and saline, were to act as discriminative conditions. The substance administered, as well as the required choice, was alternated on successive days. The drugs were administered ten minutes prior to each training session, as training occurred during the period of maximum amphetamine effect. Because of the identical side compartments, the rat could make a correct choice only by employing its current drug state as a discriminative stimulus. Each rat was trained until it made 8 out of 10 correct consecutive first choice responses (i.e., correct compartment entered) contingent upon the drug, either amphetamine or saline, that it was injected with.

2.4. Test trials with other drugs

After a rat's performance attained the criterion of 8 out of 10 consecutive first choice responses with each drug, it indicated that the rat had learned to discriminate the amphetamine drug state from the saline condition, and the rat was given testing trials with drugs other than amphetamine. Training trials were continued, with amphetamine and saline administered in random order, on Mondays, Wednesdays and Fridays. On these days, only the rats' first response was considered in counting their choice as correct or incorrect, but the rats were given 7 additional trials to maintain training. Tuesdays and Thursdays were testing days, on which other drugs were administered to observe which compartment the rats initially chose to enter. One test trial was given per day and shock was terminated upon entrance into either side compartment. Test trial performance was only accepted as data if the rat maintained the 8 out of 10 criterion on training days. If a rat fell below criterion, it was retrained for 2 weeks and any data previously obtained on it were deleted from the following results.

2.5. Selection of doses

The dosages of administered drugs used in this study were chosen as a result of previous investiga-

tions in this and other laboratories. The 0.4 mg/kg dose of nicotine was used to succesfully train rats to discriminate between nicotine and saline in a T-maze apparatus (Schechter and Rosecrans, 1971a), and the (0.048 mg/kg) LSD dose was, likewise, employed to train rats to distinguish between LSD and saline in a similar task (Schechter and Rosecrans, 1971b). The dose range of (7.43–29.72 mg/kg) mescaline was administered in this latter investigation and 22.29 and 29.72 mg/kg mescaline was observed to produce a cueing effect statistically similar to the 0.048 mg/kg LSD training dose.

l-Amphetamine has been shown to be half as potent as d-amphetamine in eliciting a compulsive gnawing syndrome in rats (Taylor and Snyder, 1971) and the selection of 4.0 and 8.0 mg/kg l-amphetamine as the testing dosages was made on this basis. Administration of 4.5 mg/kg i.p. of both d-amphetamine and fenfluramine produced similar reductions in food consumption during a 5-hr feeding period in rats, and 10 mg/kg fenfluramine was the minimum dose observed to cause a reduction in motor activity (Yelnosky and Lawlor, 1970).

2.6. Drugs

Mescaline HCl, and d- and l-amphetamine sulfate were purchased from Aldrich Chemical Co., Inc., Cedar Knoll, N.J. LSD tartrate was obtained from National Institute of Mental Health. Fenfluramine was provided by A.H. Robins Research Labs. All drugs were dissolved in 0.9% saline and administered i.p. 10 min prior to the start of a daily session at a constant volume of 1 ml/kg b.wt.

3. Results

3.1. Administration of nicotine and mescaline

The results of discrimination trials on testing-training days with 4.0 mg/kg d-amphetamine and saline, as well as responses made after 0.4 mg/kg nicotine and four doses of mescaline are presented in table 1, part 1. In 10 trials in each of eight rats after saline administration, the saline-correct compartment was entered in 67 cases, whereas the amphetamine-correct compartment was first entered in 13 trials. After 80 trials with d-amphetamine, the amphetamine-correct compartment was entered in 69 cases, whereas, the saline compartment was incorrectly chosen in 11 trials.

Table 1
Effect of nicotine, mescaline, ℓ-amphetamine and LSD on a discrimination between d-amphetamine and saline.

Drug	Dose (mg/kg)	No. of rats	No. of trials	% Responses into amphetamine compartment
Part 1				
d-Amphetamine	4.0	8	80	86.3[a]
Saline	–	8	80	16.2[b]
Nicotine	0.4	8	16	6.3[b]
Mescaline	7.43	8	8	12.5[b]
	14.86	8	8	12.5[b]
	22.29	8	8	12.5[b]
	29.72	8	8	12.5[b]
Part 2				
d-Amphetamine	4.0	10	70	90.0[a]
Saline	–	10	70	8.9[b]
ℓ-Amphetamine	4.0	10	20	70.0
	8.0	10	20	85.0
Fenfluramine	4.0	10	20	0.0[b]
	8.0	10	20	0.0[b]
LSD	0.048	10	10	5.0[b]

[a] Probability of difference from corresponding saline score being due to chance; $p < 0.001$. χ^2 test.
[b] Probability of difference from corresponding d-amphetamine (4.0 mg/kg) score being due to chance; $p < 0.001$. χ^2 test.

Nicotine, at a 0.4 mg/kg dose, was administered to each of the eight rats on two occasions, and produced only one response into the amphetamine-correct compartment, with the remaining fifteen responses being made into the saline-correct compartment. After a single administration of mescaline in doses of 7.43, 14.86, 22.29 and 29.72 mg/kg to each rat, the amphetamine compartment was chosen in 1 out of 8 trials at each dose. The percentage of first choice responses into the amphetamine-correct compartment after 0.4 mg/kg nicotine (6.3%), and all doses of mescaline (12.5%), was significantly lower than after amphetamine administrations (86.3%).

3.2. Administration of l-amphetamine, fenfluramine and LSD

The results of discrimination trials in ten rats after 4.0 mg/kg d-amphetamine and saline, as well as responses following 4.0 and 8.0 mg/kg l-amphetamine, 4.0 and 8.0 mg/kg fenfluramine and 0.048 mg/kg LSD, are presented in table 1, part 2. In this series of experiments, d-amphetamine administered in 70 trials produced 63 first choice responses into the amphetamine-correct compartment, whereas saline, in the same number of trials, produced 64 responses into the saline-correct compartment.

The 4.0 mg/kg dose of l-amphetamine, administered to each rat on 2 occasions, elicited 14 out of 20 responses into the d-amphetamine-correct compartment. The higher dose of the l-isomer (8.0 mg/kg) produced 17 out of 20 responses into the d-amphetamine compartment, which was similar to that produced after the 4.0 mg/kg training dose of d-amphetamine (90.0%). Following 2 trials in each rat at each of the 2 doses of fenfluramine, however, all responses were made into the saline-correct compartment. Copious salivation and piloerection were observed in rats following the higher (8.0 mg/kg) dose of fenfluramine, and the possibility of toxic effects precluded use of higher dose. Administration of 0.048 mg/kg LSD to each rat on 2 occasions produced 1 out of 20 responses into the amphetamine-correct compartment.

4. Discussion

Although nicotine has been shown to produce effects similar to amphetamine in behavioral tests in laboratory animals (Wanner and Battig, 1966; Morrison, 1967), and has been suggested to act via a common mechanism (Orsingher and Fulginiti, 1971), nicotine administered to rats trained to discriminate between d-amphetamine and saline did not produce an amphetamine-like cue. Previous studies (Morrison and Stephenson, 1969; Schechter and Rosecrans, 1971c) with rats trained to discriminate between nicotine and saline, reported the inability of d-amphetamine, administered in doses of 0.4 to 4.0 mg/kg, to produce a nicotine-like cue. It appears that although amphetamine and nicotine have CNS stimulant properties, the interoceptive cues produced by them in rats were not the same.

Fenfluramine has also been shown to be similar to amphetamine in its pharmacological effects (Franko et al., 1965; Alphin and Ward, 1969), but unlike amphetamine, fenfluramine acts as a depressant when administered in equal doses to rats (Yolinsky and Lawlor, 1970). In the present study, fenfluramine did not elicit a single amphetamine-like response after 40 trials at two doses. This observation indicates that the interoceptive cues produced by fenfluramine are very different from those produced by amphetamine, suggesting that fenfluramine might, indeed, be producing a cortical depressing effect in the rat.

The administration of the two hallucinatory drugs, mescaline and LSD, likewise, also failed to produce an amphetamine-like cueing effect. This confirms observations made earlier (Schechter and Rosecrans, 1971b) in which mescaline and psilocybin, but not amphetamine, produced stimulus properties similar to LSD. Thus, at least in terms of the interoceptive cues produced, these above drugs appear to be affecting different neuronal systems.

On the other hand, similar responses observed after the administration of d-amphetamine did occur after administration of the 8.0 mg/kg dose of l-amphetamine. In a comparison of the behavioral effects of the d- and l-isomers of amphetamine, Taylor and Snyder (1971) recently reported that d-amphetamine was 10 times as potent as l-amphetamine in enhancing locomotor activity in rats, but only twice as active in evoking compulsive gnawing behavior. These authors explain these dose-related dissimilarities in behavioral effects by suggesting that brain norepinephrine is selectively involved in mediating amphetamine-induced locomotor stimulation whereas a central dopaminergic system may participate in eliciting the compulsive gnawing syndrome. Since the data presented here indicated that the d- and l-isomers produced almost equivalent behavioral effects, it might be suggested that the cueing effect of amphetamine was mediated by dopaminergic neurons. However, before any definite conclusions can be made, more experimentation is needed, particularly specific dopaminergic antagonism studies.

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