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Drug Discrimination Analysis of Pseudoephedrine in Rats

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TONGJAROENBUANGAM, W., D. MEKSURIYEN, P. GOVITRAPONG, N. KOTCHABHAKDI AND B. A. BALDWIN. *Drug discrimination analysis of pseudoephedrine in rats.* PHARMACOL BIOCHEM BEHAV **59**(2) 505–510, 1998.—Rats were trained to discriminate amphetamine, 1 mg/kg given intraperitoneally, from saline injection in a two-lever operant drug discrimination task. Pseudoephedrine (a sympathomimetic drug with central and peripheral actions) at doses of 10 mg/kg failed to substitute for amphetamine, at 20 mg/kg partial substitution occurred, while at a 40 mg/kg full substitution was seen. The specificity of the amphetamine cue at the training dose used (1 mg/kg) was shown by the finding that a peripherally acting sympathomimetic drug phenylephrine at doses from 0.2 to 0.8 mg/kg failed to substitute for amphetamine. The potential for abuse of pseudoephedrine administered at high doses is discussed. © 1998 Elsevier Science Inc.

Rats Drug discrimination Pseudoephedrine Amphetamine

PSEUDOEPHEDRINE is a sympathomimetic drug whose structure and pharmacological actions are similar to those of amphetamine, a psychomotor stimulant. It is formulated in combination with other drugs and used in nonprescription decongestants, anorectic agents, and as an amphetamine substitute (2,3). The peripheral action of pseudoephedrine is reduction of tissue hyperemia, edema, and nasal congestion. Besides the peripherally mediated properties, a CNS-stimulating action of ephedrines has also been suggested. For example, investigations of the activity of amphetamines (*d*- and *l*-), ephedrines (*d*- and *l*), and *d*- and *l*-pseudoephedrines found that they were effective in eliciting turning behavior (6,18,24). However, the turning behavior induced by pseudoephedrine was less than that observed after amphetamine. In addition, this turning was not reduced by FLA63, the dopamine-β-hydroxylase inhibitor, but was practically abolished by α-methyl-*p*-tyrosine (6). These results suggested that ephedrines did not act directly, but rather were dependent on the continuing synthesis of dopamine, but not of norepinephrine.

The present experiments are concerned with comparisons between pseudoephedrine and amphetamine in an operant drug-discrimination assay. Goudie and Leathley (11) considered that the action of drugs as discriminative stimuli in animals is closely related to their subjective effects in humans, and that the discriminative properties in rats of amphetamine are related to the euphoriant and other subjective effects that humans experience after taking amphetamine. The subjective effects of drugs in humans are considered to play a major role in determining whether a drug has the potential to be abused, and animal studies of the discriminative properties of drugs may indicate which drugs are liable to be abused (5,11,20,23). The structural and pharmacological similarity of pseudoephedrine to amphetamine has made it worthwhile to further evaluate its psychomotor stimulant properties. In the present study, a drug discrimination assay in rats has been used to determine whether the internal cues arising from pseudoephedrine resemble those of amphetamine.

METHOD

Animals

The experimental animals were male Sprague–Dawley rats from the Mahidol Animal Center and weighing 170–190 g at the beginning of the experiments. Rats were housed four per cage, and maintained at room temperature under a 12 L:12 D cycle (lights on at 0700 h). Experimental sessions were conducted dur-

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ing the light phase. Tap water was available ad lib; access to dry powdered laboratory chow was restricted to 10 g/day, which was made available approximately 1 h after each operant session. Rats were run in the operant sessions 5 days a week.

Apparatus

Daily experimental sessions were conducted in a modular small-animal test cage (model E 10-10RF; Coulbourn Instruments Co. Inc., Lehigh Valley, PA), which contained two rodent levers, spaced 16 cm apart. In between the levers, a recessed food trough, to which a feeder delivered 45-mg food pellets (Bio-serv, Frenchtown, NJ), was mounted 2 cm above the cage floor. Experimental control and data collection were accomplished with a BBC personal computer programmed with Paul Fray Ltd. (UK) SPIDER Software.

Drugs

The drugs used in these experiments were: (+)-pseudoephedrine hydrochloride, phenylephrine (Sigma Chemical Company, St. Louis, MO) diazepam (Valium Roche Co., Switzerland) and d-amphetamine sulfate (Food and Drug Administration of Thailand). All drugs were dissolved in 0.9% saline, and were injected intraperitoneally in a volume of 1 ml/kg body weight, except diazepam, which was diluted with 0.9% saline containing 10% alcohol. All drugs were freshly prepared as aqueous solutions, and drug doses were calculated in terms of the free base. The dosages of pseudoephedrine hydrochloride (10–40 mg/kg) and phenylephrine (0.2–0.8 mg/kg) were selected on the basis of pilot experiments. All drug injections were given 30 min prior to the operant sessions.

Training Procedure

Behavioral training and testing consisted of three sequential stages: initial training to bar presses followed by two-bar shaping, discrimination training, and finally generalization tests. Lever pressing was established using a fixed-ratio 1 (FR1—one press for each reward) schedule of food reinforcement, followed by two-bar shaping on an FR1 schedule, progressing to an FR10 schedule, where it was maintained.

Each rat was run once a day in a 30-min session at the same time of the day, for 5 consecutive days per week. To orient the animal to the lever-pressing task and to ensure that it was situated between the two levers at the beginning of the session, one food pellet was placed in the food cup before placing the animal in the chamber. Levers were cleaned between animals with 10% ethanol solution to avoid olfactory cues (16).

Discrimination Training

In the training sessions, amphetamine or saline injections were given daily according to two weekly alternating sequences. The first sequence was amphetamine-saline-saline-amphetamine-amphetamine. The second sequence was saline-amphetamine-amphetamine-saline-saline. Thirty minutes before being introduced into the test cage, the rat was injected intraperitoneally with either 1 mg/kg amphetamine or 1 ml/kg saline. The injection technique was the same for both substances to avoid giving the rat any extra cues. According to whether the animal was injected with amphetamine or saline, to obtain food it was required to press either the amphetamine lever or the saline lever. Completion of 10 responses on the appropriate lever resulted in a 45-mg food pellet being delivered to the food cup. Responses on the inappropriate lever also were recorded throughout the session. Lever selection was said to be correct if the animal made fewer than 10 responses on the inappropriate lever before completing 10 responses on the appropriate lever (symbol: FRF $\leqslant$ 19). The FRF value is the total number of responses before the first reinforcement. An FRF of 10 indicates that the rat made 10 responses on the lever delivering reward and none on the inoperative lever prior to the first reward. In four rats, the left lever was assigned to be the amphetamine lever, the right lever being the saline lever. In another four rats, the lever assignments were reversed. Training continued until the criterion was reached. The criterion being that in each of 10 consecutive sessions a maximum of two responses were made on the inappropriate lever before 10 responses were made on the appropriate lever (FRF $\leqslant$ 12) (7,8).

Generalization Testing

When the rats had met the criterion, generalization test sessions were held each week on Wednesday and Friday. On intervening days baseline training sessions were continued to maintain discriminative control by the training drug. In the test sessions, the rats were intraperitoneally injected with pseudoephedrine hydrochloride, and were then allowed to select one of the two levers in a 30-min session. In these tests, the lever on which the rat first totaled 10 responses was regarded as the "selected lever," and subsequent reinforcement was made available for every 10th response on this lever (8,10,17). The doses of pseudoephedrine used were 10, 20, and 40 mg/kg, and they were given in descending order 30 min before the test session.

Initial tests were concerned with establishing a dose–response relation for the pseudoephedrine hydrochloride cue. Each point on the dose–response function for pseudoephedrine was determined four times. The specificity of the amphetamine or pseudoephedrine cues was examined in experiments in which the rats were injected with a different type of psychoactive drug (diazepam) and in tests with phenylephrine a drug more closely related to pseudoephedrine.

Data Analysis

For each rat, the overall response rate (responses per minute) and the percentage of responses occurring on the amphetamine-appropriate lever were calculated. The mean values were calculated for each measurement at each drug dose tested.

Data from the drug discrimination study were scored in a quantal fashion, with the lever on which the rat first completed 10 presses in a test session scored as the selected lever. The percentage of rats selecting the drug lever (%SDL) for each dose of test compound was determined. The degree of substitution was determined by the maximum % SDL for all doses of the test drug. "No substitution" was defined as 59% SDL or less, "partial substitution" was 60–79% SDL, and complete substitution was 80% or higher (16).

ANOVA followed by Dunnett's Multiple Comparison Test or paired *t*-test were used to compare between-mean values of the number of responses on the amphetamine and saline levers at each dose of the drugs.

RESULTS

Acquisition of Discrimination

When the rats were fully trained on the two-lever FR10 schedule, discrimination training was begun and most rats selected the incorrect lever during the first amphetamine training session. The rats took about 3 weeks of training (mean

14.63 ± 3.38 sessions) before reaching the discrimination training criterion, which was a maximum of two responses on the incorrect lever in each of 10 consecutive sessions. Eventually, all rats selected the amphetamine lever (AL) after being injected with amphetamine sulfate, and selected the saline lever (SL) after saline injection. Following the training sessions, all rats were run five times a week in control sessions. Correct lever selection remained very constant and accurate.

It was found that amphetamine (1 mg/kg) significantly reduced the response rate per minute of lever pressing for food when compared with the rate seen after saline injection (amphetamine 39.48 ± 5.31; saline 57.38 ± 3.83). This consistent and significant (Dunnett's Multiple Comparison Test, $p < 0.01$) reduction in response rate produced by the standard dose (1 mg/kg) of amphetamine sulfate was seen in all rats.

Generalization Tests

After the rats had been trained to meet a criterion of 10 consecutive sessions of correct lever selection with FRF ⩽ 12, generalization tests were initiated. At a dose of 40 mg/kg of pseudoephedrine a 90% drug-lever selection was observed (i.e., three selections of the saline lever compared with 28 on the amphetamine lever, Table 1). At doses of pseudoephedrine of 10 and 20 mg/kg, the percentages of drug-lever selection were 50 and 75%, respectively (Table 1).

During generalization tests with pseudoephedrine at doses of 10, 20, and 40 mg/kg, the average FRF values following injections of saline were 10.18 ± 0.09, 10.25 ± 0.11, and 11.58 ± 0.78, respectively, while the average FRF values following injections of amphetamine were 10.54 ± 0.46, 10.08 ± 0.08, and 10.87 ± 0.39, respectively. Testing with pseudoephedrine was carried out the next day on the rare occasions when a rat had an FRF ⩽ 13 following saline or amphetamine. However, this only occurred 6 times during 144 injections and on only one of their of these occasions was an FRF ⩽ 13 seen when pseudoephedrine was administered next day.

The response rate of pseudoephedrine-dosed rats on the amphetamine or saline levers is illustrated in Fig. 1 . The response rate on the amphetamine lever of rats dosed with pseudoephedrine at 10, 20, and 40 mg/kg was not significantly different from the response rate on the amphetamine lever when the rats had received 1 mg/kg amphetamine (control). The response rate on the saline lever after pseudoephedrine at 10 mg/kg was significantly different from the response rate after saline injection ($p < 0.05$), and at doses of 20 and 40 mg/kg the response rate was also significantly different from the rate after saline injection ($p < 0.01$) (Fig. 1). The rate of response on the saline lever decreased in a dose-dependent manner but the response rate on the amphetamine levers did not increase in the dose-dependent manner.

The total response rate (combined rates on both levers) after dosing with saline or amphetamine are shown in Fig. 2 and it is apparent that rate is significantly lower ($p < 0.01$) after injection of amphetamine. The total response rate after dosing with pseudoephedrine at 10 and 20 mg/kg were similar to the total response rate following saline injection (Fig. 2). By contrast, after dosing with pseudoephedrine at 40 mg/kg, the total response rate was significantly reduced ($p < 0.01$). As can be seen in Fig. 2 the total response rate following 40 mg/

TABLE 1
THE ACTION OF PSEUDOEPHEDRINE ON RATS TRAINED IN THE AMPHETAMINE–SALINE DISCRIMINATION PROCEDURE

Pseudoephedrine (mg/kg) IP	Rat No.	Number of Experiments	Lever Selection		FRF		% SDL	
			Saline	Amphetamine	Range	Mean	%	Mean
10	1	4	4	0	10–10	10.0	0	
10	2	4	3	1	10–16	13.0	25	
10	3	4	0	4	10–12	10.5	100	
10	4	4	4	0	10–18	15.0	0	50%
10	5	4	4	0	10–11	10.5	0	
10	6	4	0	4	10–12	10.5	100	
10	7	4	0	4	10–11	10.3	100	
10	8	4	1	3	10–12	10.5	75	
20	1	4	2	2	10–14	11.5	50	
20	2	4	0	4	10–11	10.3	100	
20	3	4	0	4	10–10	10.0	100	
20	4	4	0	4	10–10	10.0	100	75%
20	5	4	4	0	10–17	11.8	0	
20	6	4	2	2	14–16	15.0	50	
20	7	4	0	4	10–13	11.0	100	
20	8	4	0	4	10–10	10.0	100	
40	1	3	1	2	10–16	12.0	66.7	
40	2	4	0	4	10–10	10.0	100	
40	3	4	0	4	10–15	11.8	100	
40	4	4	0	4	10–11	10.5	100	90.32%
40	5	4	2	2	10–10	10.0	50	
40	6	4	0	4	10–15	11.3	100	
40	7	4	0	4	10–10	10.0	100	
40	8	4	0	4	10–10	10.0	100	

mean FRF = total number of presses on both levers, made before obtaining the first food pellet.
% SDL = % selection drug lever (amphetamine lever) for the first reward (FRF) calculated from columns 4 and 5.

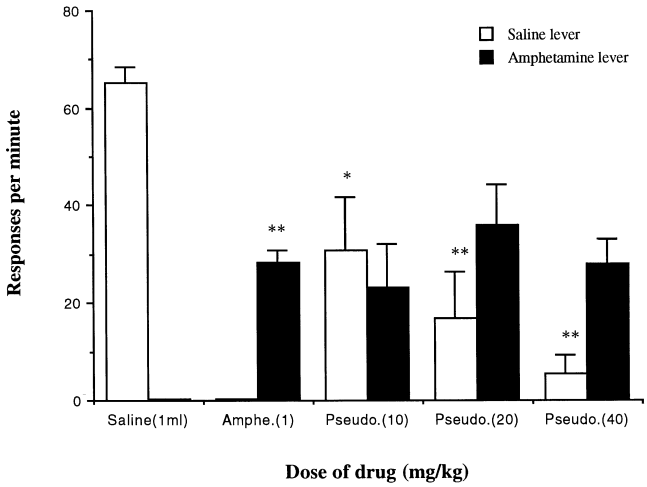

FIG. 1. This figure illustrates the responses per minute (mean ± SEM) on the amphetamine lever or the saline lever. The first two columns represent response rates in control sessions after saline and amphetamine (Amphe.) injection in rats trained to discriminate 1 mg/kg amphetamine (Amphe.) from saline. The response rates after amphetamine injection were significantly less ($p < 0.01$) than the rates after saline injection. The final three columns show the response rates seen after pseudoephedrine (Pseudo.) at 10, 20, and 40 mg/kg during generalization tests occurring at the same time as the saline and amphetamine treatment shown in the first two columns. There was no significant difference between control response rates on the amphetamine lever and response rates on this lever after being given different doses of pseudoephedrine. Significant differences occurred between control response rates on the saline lever and response rates on this lever after being given different doses of pseudoephedrine ($*p < 0.05$, $**p < 0.01$).

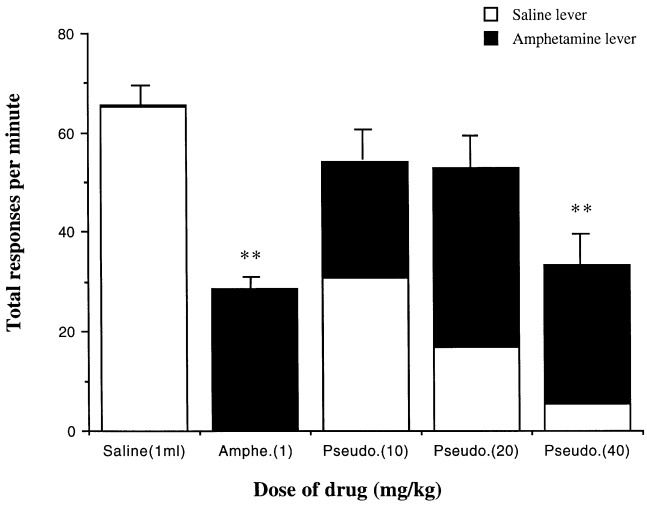

FIG. 2. This figure illustrates the mean and SEM of the total responses per minute (i.e., combined response rate on both amphetamine and saline levers). The first two columns represent total responding rates in control sessions after saline and amphetamine (Amphe.) injections. The final three columns represent the total response rates of rats dosed with 10, 20, and 40 mg/kg pseudoephedrine (Pseudo.). A significant difference ($**p < 0.01$) was observed between the total response rates in control sessions after saline and the rates after being dosed with 1 mg/kg amphetamine or with 40 mg/kg pseudoephedrine.

kg of pseudoephedrine was not significantly different from the total response rate seen after 1 mg/kg amphetamine.

Finally, to test the specificity of the drug discrimination assay used in these experiments, the rat were dosed with two drugs with markedly different pharmacological properties. The first substance used was diazepam, a powerful CNS drug with anxiolytic properties that would produce an interoceptive cue different from that produce by amphetamine. Diazepam was given IP at a dose of 1 mg/kg, a dose that has previously been shown to produce an effective discriminative stimulus in a drug discrimination experiment (1). In the present experiments it was found that all the rats dosed with diazepam selected the saline lever. The vehicle used in the diazepam experiments (10% alcohol in 0.9% saline) was also tested in discrimination assays, and all the rats selected the saline lever.

The second drug tested was phenylephrine, a sympathomimetic agent that does not readily enter the central nervous system but produces peripheral cardiovascular effects by acting on a adrenergic receptors in vascular smooth muscle. Its cardiovascular effects are similar to the peripheral effects of pseudoephedrine (13). The results obtained with phenylephrine are shown in Table 2, from which it is apparent that, at doses of 0.2, 0.6, and 0.8 mg/kg given IP, the rat almost exclusively selected the saline lever. Measurement of the rate of responding on the saline lever revealed that at doses of 0.6 and 0.8 mg/kg the response rates (69.28 ± 1.50 and 59.53 ± 4.60, respectively) were significantly less than when saline was injected ($p < 0.05$ and $p < 0.01$ Dunnett's multiple comparison test). In preliminary experiments it was found that a dose of 1 mg/kg rendered the rats immobile for 30–45 min postinjection.

DISCUSSION

The effects of amphetamine (training drug) have been investigated in a drug discrimination paradigm. This paradigm is a "detection" procedure that has been found useful for the

TABLE 2
THE ACTION OF PHENYLEPHRINE ON RATS TRAINED IN THE AMPHETAMINE–SALINE DISCRIMINATION PROCEDURE

Phenylephrine (mg/kg) IP	Number of Rats (n)	Number of Experiments	Lever Selection		FRF		Mean % SDL	Mean Number of Responses per Minute (± SEM) on Saline Lever
			Saline	Amphetamine	Range	Mean		
0.2	7	14	14	0	10–13	10.29	0	74.62 ± 3.45
0.6	7	14	14	0	10–13	10.36	0	69.28 ± 1.50
0.8	7	14	13	1	10–11	10.21	7.14	59.53 ± 4.60

mean FRF = total number of presses on both levers, made before obtaining the first food pellet.
% SDL = % selection drug lever (amphetamine lever) for the first reward (FRF) calculated from columns 4 and 5.

study of the effects of drugs which act on the central nervous system and has been used to train animals to discriminate between the presence or absence of the effects produced by the drugs, in this case, amphetamine sulfate (1 mg/kg). The rats learn to guide their behavior on the basis of the presence or absence of the drug. They learned to make one response (drug-appropriate response) to obtain a food reward when influenced by the drug, and to make the other response (the no-drug response) when not influenced by the drug's internal stimulus.

When comparison is made between the response rate allocated between the saline lever and the amphetamine lever following saline or amphetamine injection, respectively, it can be seen that the response rate after amphetamine injection decreased significantly ($p < 0.01$) (Fig. 1).

The results of the generalization tests demonstrated that pseudoephedrine can produce a discriminative stimulus similar to that of amphetamine. After treatment with pseudoephedrine, rats previously trained with amphetamine displayed increases in their relative amount of responding on the amphetamine lever compared with the saline lever (Fig. 1). The data presented in Table 1 were interpreted using the scoring system suggested by Nichols et al. (16) and indicates that at the lowest dose (10 mg/kg pseudoephedrine) no substitution was seen [% selection of amphetamine lever (%SDL) was 50%]. When dosed with 20 mg/kg pseudoephedrine the %SDL was 75%, which would qualify as partial substitution, while full substitution was displayed at a dose of 40 mg/kg, with a %SDL of 90%. These results indicate that while pseudoephedrine produces a discriminative stimulus resembling that of amphetamine, it is less potent than amphetamine as 40 mg/kg were required for full substitution.

Evidence that the central effects of pseudoephedrine and not its peripheral actions provided a discriminative stimulus similar to that of amphetamine was obtained in the experiments using phenylephrine. Phenylephrine, another sympathomimetic agent, produces similar peripheral cardiovascular effects to pseudoephedrine but does not readily enter the central nervous system (13). It was shown that phenylephrine, at a dose range up to 0.8 mg/kg, failed to substitute for amphetamine in generalization tests (Table 2).

There is some evidence, from studies by Snoddy and Tessel (19), that the nature of the discriminative stimulus produced by amphetamine depends upon the dose and that high doses such as 3.2 mg/kg produce a stimulus that is qualitatively different from that produced by a low dose of 1 mg/kg. They suggested that at 1 mg/kg the discriminative stimulus could depend upon the central release of norepinephrine while at 3.2 mg/kg the stimulus could be due to release of both norepinephrine and dopamine.

The failure of diazepam to substitute in the discrimination test for amphetamine indicates that its centrally produced discriminative stimulus differs from that produced by either amphetamine or pseudoephedrine. The result provides further supporting evidence that the drug discrimination procedure used in the present experiments was specific for substances resembling the training drug.

Many addictive drugs such as amphetamine have a psychostimulant action that contributes to the rewarding actions (21). It is accepted that analysis of the discriminative properties of drugs in relation to the discriminative stimuli produced by known drugs of abuse can be useful in predicting which drugs may be liable to abuse (5,11). The present results suggest that pseudoephedrine may have an abuse potential when administered at high doses.

There is evidence that the rewarding properties of amphetamines act through an interaction with the mesolimbic dopamine system, which involves dopaminergic projections from the ventral tegmental area in the midbrain to the nucleus accumbens in the basal forebrain (4,9,14,22). The discriminative stimulus properties of amphetamine are thought to be mediated primarily through the dopaminergic system (12,15). Ephedrines have been shown to induce the release and block the uptake of dopamine in vitro, as well as inducing behavioral effects thought to reflect increased dopaminergic activity (24–26).

Recent work in this laboratory (Srisawat et al., unpublished observation) has shown that pseudoephedrine can act upon the dopaminergic system by inducing an increase in dopamine metabolites in the rat striatum and nucleus accumbens. Further work is needed to establish the neurochemical actions of pseudoephedrine and determine whether they resemble those of amphetamine. The present findings in the drug discrimination assay demonstrate that, at high doses, pseudoephedrine can produce a discriminative stimulus similar to that of amphetamine.

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