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Stimulus Effects of Phenylpropanolamine Optical Isomers in (+)Amphetamine-Trained Rats

RICHARD YOUNG AND RICHARD A. GLENNON

Department of Medicinal Chemistry, School of Pharmacy, Box 980540, Virginia Commonwealth University, Richmond, VA 23298

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YOUNG, R. AND R. A. GLENNON. *Stimulus effects of phenylpropanolamine optical isomers in (+)amphetamine-trained rats.* PHARMACOL BIOCHEM BEHAV **66**(3) 489–494, 2000.—There are eight phenylpropanolamine optical isomers related in structure to the central stimulants methamphetamine and amphetamine. Some of these are quite well known, such as (−)ephedrine, whereas others are relatively obscure, such as (−)cathine. Although certain of these phenylpropanolamines, such as (−)ephedrine and (+)cathine, retain central stimulant activity and are about 10- to 25-fold less potent than (+)amphetamine, the eight phenylpropanolamines have been compared only once before in drug discrimination studies. This latter study employed (−)ephedrine as the training drug. Because there are striking similarities between (−)ephedrine and (+)amphetamine as training drugs, it was of interest to determine and compare the effect of all eight phenylpropanolamines in (+)amphetamine trained animals. Using rats trained to discriminate 1 mg/kg of (+)amphetamine from saline vehicle under a variable interval 15-s (VI 15-s) schedule of reinforcement, the (+)amphetamine stimulus generalized only to (−)ephedrine (ED_{50} = 4.5 mg/kg) and (+)cathine (ED_{50} = 8.0 mg/kg), and both agents were at least 10 times less potent that (+)amphetamine (ED_{50} = 0.37 mg/kg). These results stand in contrast to those obtained with the (−)ephedrine-trained animals where the ephedrine stimulus generalized to all of the phenylpropanolamines except for (−)pseudoephedrine and (−)cathine. It is concluded that although there might be some similarity between the (−)ephedrine and (+)amphetamine stimuli, there are clear differences between them as determined in tests of stimulus generalization under the conditions employed. © 2000 Elsevier Science Inc.

Phenylpropanolamines Ephedrine Norephedrine Pseudoephedrine Pseudonorephedrine Cathine Amphetamine Ephedra Khat

INTRODUCTION of a hydroxyl group at the β-position of methamphetamine and amphetamine affords a series of agents generically referred to as phenylpropanolamines. This change in structure also introduces a second asymmetric center such that there are now two chiral centers, rather than one, in each molecule. This means that there are eight possible optical isomers of these phenylpropanolamines. The β-hydroxyl analogs of methamphetamine are (−)ephedrine, (+)ephedrine, (−)pseudoephedrine, and (+)pseudoephedrine, whereas the corresponding structural alteration of amphetamine results in (−)norephedrine, (+)norephedrine, (−)cathine [also known as (−)pseudonorephedrine] and (+)cathine [or (+)pseudonorephedrine].

Over the past decade there has been a resurgence of interest in ephedrine-related agents because of their ready over-the-counter availability (7), and their use as thermogenic agents (1,3) and as herbal dietary supplements (8) [see Young et al. (20) for additional discussion]. Many of these preparations use ephedra (*Ephedra sinica*) as their active constituent, and ephedra is known to contain several different phenylpropanolamines, with (−)ephedrine being the predominant isomer (11). (+)Cathine, found as a minor constituent in *Ephedra sinica*, is also a component of the shrub khat or *Catha edulis* (13,15). Khat is employed for its central stimulant actions, and although the most abundant stimulant component of fresh khat leaves is cathinone (i.e., an oxidation product of

Requests for reprints should be addressed to Richard A. Glennon, Department of Medicinal Chemistry, Box 980540 VCU, Richmond, VA 23298.

cathine), (+)cathine itself has been demonstrated to produce a stimulant action in animals (4).

With the increasing popularity of these over-the-counter agents, and with reports that they can produce amphetamine-like central stimulation (as well as amphetamine-like toxicity) in humans (7), it was of interest to determine which of the phenylpropanolamines is capable of producing an amphetamine-like stimulus effect in animals. There have been only two previous reports comparing all eight isomers in the same study. More than 30 years ago Fairchild and Alles (4) found that several of the phenylpropanolamines are locomotor stimulants in mice. Their potencies followed the order: (+)cathine > (−)ephedrine > (−)cathine; the remaining agents produced locomotor stimulation only at or near their lethal doses precluding accurate potency comparisons. Specifically, (+)cathine was twice as potent as (−)ephedrine, and (−)cathine was half as potent as (−)ephedrine; for purpose of comparison, (+)cathine itself was 10 times less potent than (+)amphetamine. In a more recent investigation of the eight optical isomers, all, except for (−)pseudoephedrine and (−)cathine, produced ephedrine-like stimulus effects in rats trained to discriminate 4 mg/kg of (−)ephedrine from saline vehicle in a drug discrimination procedure. In the latter study, the order of potency was shown to be (−)ephedrine > (−)norephedrine > (+)ephedrine > (+)cathine > (+)norephedrine > (+)pseudoephedrine (20). Although this study provides the most comprehensive comparative data to date, it cannot be assumed on the basis of these results that the amphetamine-like nature of these agents would necessarily have the same rank order of potency. For example, methamphetamine is at least as potent as, if not more potent than, amphetamine in tests of stimulus generalization using rats trained to discriminate (+)amphetamine from vehicle [reviewed: (18)]. However, administration of (+)methamphetamine to (−)ephedrine-trained animals failed to result in ephedrine-stimulus generalization even though the (−)ephedrine stimulus generalized to (+)amphetamine, cocaine, and other central stimulants (20). Furthermore, we have already demonstrated that (a) (−)ephedrine but not (+)ephedrine results in (+)amphetamine-stimulus generalization, and that (b) (−)ephedrine is half as potent as (+)amphetamine in (−)ephedrine-trained animals but is only one-tenth as potent as (+)amphetamine in (+)amphetamine-trained animals (20). Thus, although there are distinct similarities between the ephedrine and the amphetamine stimuli, there appear to be marked differences. In the present investigation we compare all eight phenylpropanolamine isomers in rats trained to discriminate (+)amphetamine from saline vehicle to determine (a) which isomers are capable of producing amphetamine-like stimulus effects, and (b) the relative potencies of the isomers in this regard. A (+)amphetamine training dose of 1 mg/kg was selected because it is the most common training dose employed for this agent when rats are used as subjects [reviewed: (18)]. A subsequent goal of this work was to identify any additional differences (if any) that might exist between the stimulus effects produced by (−)ephedrine and (+)amphetamine.

METHOD

Stimulus Generalization Studies

The present investigation employed a group of nine male Sprague–Dawley rats (Charles River Laboratories; Wilmington, MA) previously trained to discriminate 1.0 mg/kg of (+)amphetamine sulfate from 1.0 ml/kg of 0.9% saline solution using standard two-lever operant equipment and a variable-interval 15-s schedule of reinforcement (21). In brief, animals weighing 350–400 g at the beginning of the study, were housed individually and, prior to the start of the study, their body weights were reduced to approximately 80% of their free-feeding weight. During the entire course of the study, the animals' body weights were maintained at this reduced level by partial food deprivation. In their home cages, the animals were allowed drinking water ad lib. The rats were trained (15-min training session) to discriminate intraperitoneal injections (15-min presession injection interval) of 1.0 mg/kg of (+)amphetamine from vehicle (sterile 0.9% saline) under a variable-interval 15-s schedule of reward (i.e., sweetened milk) using standard two-lever operant chambers. The procedure and the instrumentation are the same as previously reported (21). Daily training sessions were conducted with (+)amphetamine or saline. On every fifth day, learning was assessed during an initial 2.5-min nonreinforced (extinction) session followed by a 12.5-min training session. For four of the animals, the left lever was designated the drug-appropriate lever, whereas the situation was reversed for the remaining five animals. Data collected during the extinction session included responses/min (i.e., response rate) and number of responses on the drug-appropriate lever (expressed as a percent of total responses).

Stimulus generalization studies were not begun until after the animals had been shown to reliably discriminate (+)amphetamine from vehicle (i.e., after the animals made >80% of their responses on the drug appropriate lever after administration of (+)amphetamine, and <20% of their responses on this same lever after administration of saline, for 3 consecutive weeks). In the present investigation, tests of stimulus generalization were conducted to determine if the (+)amphetamine stimulus would generalize to the various phenylpropanolamines. During this phase of the study, maintenance of the (+)amphetamine–saline discrimination was ensured by continuation of the training sessions on a daily basis (except on a generalization test day; see below). On 1 of the 2 days before a generalization test, about half of the animals would receive (+)amphetamine and about half would receive saline; after a 2.5-min extinction session, training was continued for 12.5 min. Animals not meeting the original criteria (i.e., >80% of total responses on the drug-appropriate lever after administration of training drug, and <20% of total responses on the same lever after administration of saline), during the extinction session were excluded from the immediately subsequent generalization test session. During the investigations of stimulus generalization, test sessions were interposed among the training sessions. The animals were allowed 2.5 min to respond under nonreinforcement conditions; the animals were then removed from the operant chambers and returned to their home cages. An odd number of training sessions (usually five) separated any two generalization test sessions. Doses of the test drugs were administered in a random order, using a 15-min presession injection interval (except where noted), to groups of four to nine rats. If a particular dose of a challenge drug resulted in disruption of behavior (i.e., no responding), only lower doses would be evaluated in subsequent weeks. Stimulus generalization was considered to have occurred when the animals, after a given dose of challenge drug, made ≥80% of their responses on the (+)amphetamine-appropriate lever. Animals making fewer than five total responses during the entire 2.5-min extinction session were considered as being "disrupted." Where stimulus generalization occurred, ED_{50} values were calculated by the method of Finney (6). The ED_{50} doses are doses at which the animals

would be expected to make 50% of their responses on the drug-appropriate lever.

(±)Norephedrine (i.e., racemic norephedrine) was also examined in a group of six rats that we had previously trained to discriminate 4.0 mg/kg of (−)ephedrine from saline vehicle. The training and testing procedures are essentially the same as those employed above and have been recently described in detail (19).

Drugs

(−)Ephedrine hydrochloride ([1R,2S]-(−)-2(methylamino)-1-phenylpropan-1-ol HCl), (+)ephedrine HCl ([1S,2R]-(+)-2-(methylamino)-1-phenylpropan-1-ol HCl), (+)pseudoephedrine ([1S,2S]-(+)-2-(methylamino)-1-phenylpropan-1-ol HCl), (−)pseudoephedrine ([1R,2R]-(−)-2-(methylamino)-1-phenylpropan-1-ol HCl), (−)norephedrine ([1R,2S]-(−)-2-amino-1-phenylpropan-1-ol), (+)norephedrine ([1S,2R]-(+)-2-amino-1-phenylpropan-1-ol HCl), and racemic norephedrine HCl were obtained from Sigma-Aldrich Corp (St. Louis, MO). (+)Cathine HCl and (−)cathine HCl (i.e., [1S,2S]-(+)- and [1R,2R]-(−)-amino-1-phenylpropanol, respectively) were synthesized according to the method of Fairchild and Alles (4); the (+)cathine was chromatographically identical to a sample obtained as a gift from the World Health Organization. (+)Amphetamine sulfate was on hand as a result of earlier studies.

Solutions of all drugs were made fresh daily in 0.9% sterile saline, and all agents were administered via intraperitoneal injection in a 1 ml/kg injection volume 15 min prior to testing, except where noted. All doses refer to the weight of the salt.

RESULTS

The present investigation employed a group of rats that we had reliably trained to discriminate 1 mg/kg of (+)amphetamine from saline vehicle (21). The history of these animals, including data obtained for (−)ephedrine and (+)ephedrine, was recently described (21). As reported, the amphetamine stimulus generalized to (−)ephedrine (ED_{50} = 4.5 mg/kg) but only partially generalized to (+)ephedrine [50% (+)amphetamine appropriate responding at 12 mg/kg] (21). With respect to the remaining phenylpropanolamines (see Table 1), the amphetamine stimulus generalized only to (+)cathine (ED_{50} = 8.0 mg/kg). At the highest dose examined (i.e., 16 mg/kg), (+)cathine produced about a 50% reduction in response rates. In contrast, its enantiomer, (−)cathine, elicited a maximum of 29% (+)amphetamine-appropriate responding at 4 mg/kg, 14 and 0% drug-appropriate responding at slightly higher doses (5 and 5.8 mg/kg, respectively), and disruption of behavior at 6.5 mg/kg.

(+)Norephedrine, (−)pseudoephedrine, and (+)pseudoephedrine failed to produce greater than 8% (+)amphetamine-appropriate responding at the highest nondisruption doses evaluated and, with the exception of (+)norephedrine, produced disruption of behavior as dose was further increased. (+)Norephedrine produced only 4% (+)amphetamine-appropriate responding at 30 mg/kg and higher doses were not examined because the animals' response rates were already reduced by nearly 50%.

(−)Norephedrine produced a maximum of 52% (+)amphetamine-appropriate responding (at 7 mg/kg); administration of a higher dose of this agent (i.e., 7.5 mg/kg) resulted in disruption of the animals' behavior. Racemic norephedrine also was examined and 15 mg/kg produced 59% (+)amphetamine-appropriate responding, whereas higher doses resulted in disruption of behavior (Table 1). For comparison, racemic norephedrine was additionally examined in a group of rats previously trained to discriminate 4 mg/kg of (−)ephedrine from saline vehicle. The (−)ephedrine stimulus generalized to racemic norephedrine in a dose-related manner (Table 2); (−)ephedrine (ED_{50} = 0.8 mg/kg) was about five times more potent than norephedrine (ED_{50} = 4.6 mg/kg). The animals' response rates were decreased by >65% following the dose that produced 80% (−)ephedrine-appropriate responding.

Both isomers of pseudoephedrine were also examined using a 30-min presession injection interval (Table 1). (+)Pseudoephedrine elicited a maximum of 61% (+)amphetamine appropriate responding at 15 mg/kg; at this dose only half of the animals responded and their response rates were depressed by >50%. Administration of higher doses of (+)pseudoephedrine resulted in disruption of behavior. (−)Pseudoephedrine never produced more than 0% (+)amphetamine-appropriate responding.

DISCUSSION

Consistent with their prior history as amphetamine-like central stimulants [e.g., (4)], both (−)ephedrine and (+)cathine are now shown to produce >80% (+)amphetamine-appropriate responding in rats trained to discriminate (+)amphetamine from saline vehicle (Table 1). In the present investigation, (+)cathine was about half as potent as (−)ephedrine. Fairchild and Alles (4) previously found that (+)cathine was twice as potent as (−)ephedrine as a locomotor stimulant in mice, and that (−)ephedrine was about 25-fold less potent than (+)amphetamine (4). However, although (−)cathine also produced locomotor stimulation in mice at 50 times the dose required of (+)amphetamine (4), Table 1 shows that the (+)amphetamine stimulus failed to completely generalize to this agent.

The (+)amphetamine stimulus also failed to generalize to (+)pseudoephedrine and (−)pseudoephedrine. Tongjaroenbuangam and co-workers (16) have demonstrated that at a dose of 40 mg/kg (+)pseudoephedrine substitutes for amphetamine in rats trained to discriminate 1 mg/kg of (+)amphetamine from vehicle. In the present study, administration of 11 mg/kg of (+)pseudoephedrine elicited 0% (+)amphetamine-appropriate responding. At this dose, only three of six animals made more than five total responses during the entire extinction session, and the animals' response rates were depressed (i.e., 3.6 responses/min). Administration of 13 mg/kg resulted in disruption of behavior in the majority of the animals precluding evaluation of higher doses, and the two animals that responded at this dose made only 28 and 0% of their responses on the drug-appropriate lever. One of several differences between the two studies is that the former used a 30-min presession injection interval for the training drug, whereas we used a 15-min presession injection interval throughout. We repeated the tests of stimulus generalization with both isomers of pseudoephedrine using the longer (i.e., 30 min) presession injection interval. Although the results obtained with the (−)isomer were similar regardless of presession injection interval, a difference was noted with (+)pseudoephedrine. With a 15-min presession injection interval, the animals never made more than 2% of their responses on the drug-appropriate lever. However, with the 30-min interval, administration of 15 mg/kg resulted in the animals making 61% of their responses on the (+)amphetamine-designated lever. Nevertheless, higher doses (i.e., 16.5 and 18 mg/kg) produced disruption of behavior. Thus, even with the longer pre-

TABLE 1

RESULTS OF STIMULUS GENERALIZATION STUDIES WITH PHENYLPROPANOLAMINE OPTICAL ISOMERS IN RATS TRAINED TO DISCRIMINATE 1 mg/kg OF (+)AMPHETAMINE FROM VEHICLE

Agent	Time*	Dose mg/kg	*n*†	% Drug-Appropriate Responding‡	Response Rates (Resp/min)‡
(+)Amphetamine	15	0.25	9/9	23 (8)	15.8 (3.2)
	15	0.50	9/9	74 (10)	15.3 (5.0)
	15	1.00	9/9	98 (1)	11.3 (1.9)
				ED_{50} = 0.37 (0.26–0.52)mg/kg¶	
Saline (1 ml/kg)	15		9/9	5 (2)	17.5 (3.1)
(−)Ephedrine§	15	2.0	5/5	0	17.6 (11.0)
	15	4.0	5/5	49 (16)	7.5 (2.7)
	15	6.0	4/5	65 (9)	5.5 (1.0)
	15	8.0	4/5	97 (3)	4.9 (1.2)
				ED_{50} = 4.5 (3.24–6.31) mg/kg	
(+)Ephedrine§	15	2.0	4/4	1 (1)	19.9 (5.7)
	15	4.0	4/4	10 (6)	14.0 (6.4)
	15	8.0	4/4	2 (2)	6.2 (3.0)
	15	10.0	4/4	3 (3)	10.5 (4.4)
	15	12.0	7/9	50 (16)	6.6 (1.7)
	15	13.0	7/9	43 (15)	4.2 (0.8)
	15	14.0	4/9	—#	—
	15	15.0	1/4	—‖	—
(−)Pseudoephedrine	15	3.0	6/6	0	6.5 (2.3)
	15	6.0	3/6	0	3.9 (0.6)
	15	7.5	2/6	—**	—
	30	5.0	6/6	0	5.5 (1.1)
	30	10.0	3/6	0	3.7 (0.6)
	30	15.0	2/6	—††	—
(+)Pseudoephedrine	15	3.0	6/6	0	17.0 (7.4)
	15	6.0	6/6	0	8.4 (2.8)
	15	9.0	3/6	2 (2)	8.5 (3.3)
	15	11.0	3/6	0	3.6 (0.6)
	15	13.0	2/6	—‡‡	—
	30	10.0	5/6	15 (5)	5.1 (1.3)
	30	15.0	3/6	61 (20)	4.9 (0.6)
	30	16.5	1/6	—§§	—
	30	18.0	1/6	—§§	—
(−)Norephedrine	15	5.0	5/6	4 (4)	3.8 (0.3)
	15	6.0	4/6	49 (28)	6.9 (3.2)
	15	7.0	3/6	52 (29)	2.7 (0.4)
	15	7.5	2/6	—¶¶	—
(+)Norephedrine	15	6.0	6/6	6 (4)	14.3 (3.4)
	15	12.0	6/6	1 (1)	10.5 (2.7)
	15	18.0	5/6	3 (3)	8.5 (2.2)
	15	24.0	5/6	8 (6)	5.7 (3.8)
	15	30.0	3/5	4 (4)	6.0 (3.8)
(±)Norephedrine	15	4.5	5/5	6 (5)	8.2 (3.1)
	15	9.0	5/5	4 (4)	4.7 (1.0)
	15	12.0	5/5	36 (23)	5.0 (1.5)
	15	15.0	4/5	59 (16)	3.8 (0.5)
	15	16.0	2/5	—##	—
	15	20.0	1/5	—##	—
(−)Cathine	15	2.0	6/6	4 (4)	4.0 (0.8)
	15	4.0	3/6	29 (29)	5.7 (0.8)
	15	5.0	4/6	14 (14)	4.7 (0.7)
	15	5.8	3/6	0	7.5 (2.9)
	15	6.5	0/6	—	—

(*continued*)

TABLE 1
CONTINUED

Agent	Time*	Dose mg/kg	*n*†	% Drug-Appropriate Responding‡	Response Rates (Resp/min)‡
(+)Cathine	15	4.0	4/4	22 (8)	9.8 (2.6)
	15	8.0	4/4	37 (15)	8.6 (1.4)
	15	10.0	4/4	64 (14)	7.3 (1.0)
	15	13.0	4/4	70 (10)	7.2 (1.6)
	15	16.0	3/4	89 (9)	5.4 (1.0)
				ED_{50} = 8.0 (4.9–13.1)mg/kg¶	

*Time: presession injection interval.
†*n*: number of animals responding/numer of animals administered drug.
‡Data obtained during a 2.5-min extinction session; data are followed by ±SEM in parenthesis.
§Data for (−)ephedrine and (+)ephedrine were previously reported in graphical form (21), and are reported in detail here merely for purpose of comparison.
¶ED_{50} values followed in parenthesis by 95% confidence limits.
#The four animals that responded made 50, 0, 0, and 73% of their responses on the drug-appropriate lever; response rate = 6.4, 7.2, 12.0, and 8.8 responses/min.
‖The one animal that responded made 67% of its responses on the drug-appropriate lever; response rate = 3.6 responses/min.
**The two animals that responded made 17 and 0% of their responses on the drug-appropriate lever; response rates = 2.4 and 2.8 response/min.
††The two animals that responded made 0% of their responses on the drug-appropriate lever; response rates = 2.8 and 6.0 responses/min.
‡‡The two animals that responded made 28 and 0% of their responses on the drug-appropriate lever; response rates = 7.2 and 3.6 responses/min.
§§The animals that responded at 16.5 and 18 mg/kg made 43 and 71% of their responses, respectively, on the drug-appropriate lever; response rates = 2.8 responses/min.
¶¶The two animals that responded made 0% of their responses on the drug-appropriate lever; response rates = 2.4 and 4.8 responses/min.
##The two animals that responded at 16 mg/kg made 100 and 0% of their responses on the drug-appropriate lever, whereas the animal that responded at 20 mg/kg made 100% of its responses on the same lever; response rates = 3.2, 2.4, and 3.6 responses/min, respectively.

session injection interval, the (+)amphetamine stimulus failed to completely substitute for (+)pseudoephedrine, and higher doses produced behavioral disruption. Variation between the two studies might be related to other testing parameters or procedures.

Racemic norephedrine (a.k.a. "phenylpropanolamine") was examined in the present study because conflicting reports have appeared in the literature. In one study using rats as subjects, it had been found that a (+)amphetamine stimulus generalizes to racemic norephedrine (14), whereas in two other studies, using the same species of animals, administration of racemic norephedrine resulted only in partial generalization (i.e., norephedrine produced a maximum of only 56 and 75% (+)amphetamine-appropriate responding) (10,12). Racemic norephedrine also substituted for (+)amphetamine in three of four pigeons (5) and in two of four monkeys (17). Racemic norephedrine and (+)amphetamine reportedly produce similar subjective effects in humans (2). Racemic norephedrine has also been used as a training drug and the (±)norephedrine stimulus has been demonstrated to generalize to (±)amphetamine (9); however, (+)amphetamine was not examined in that study. In the present study, racemic norephedrine produced a maximum of 59% (+)amphetamine-appropriate responding. These results are consistent with two of the three published rodent studies. Inconsistencies with the other studies may reflect the effect of species difference.

To explore possible similarities and differences between the (+)amphetamine stimulus and the (−)ephedrine stimulus, racemic norephedrine was also administered to a group of rats previously trained to discriminate 4 mg/kg of (−)ephe-

TABLE 2
RESULTS OF STIMULUS GENERALIZATION STUDIES WITH RACEMIC NOREPHEDRINE IN RATS TRAINED TO DISCRIMINATE 4 mg/kg OF (−)EPHEDRINE FROM VEHICLE*

Agent	Dose mg/kg	*n*†	% Drug-Appropriate Responding‡	Response Rates (Resp/min)
(−)Ephedrine	4.0	6/6	97 (1)	9.6 (2.0)
			ED_{50} = 0.8 (0.4–1.6) mg/kg*	
Saline (1.0 ml/kg)		6/6	4 (2)	9.8 (2.2)
(+)Norephedrine	3.0	5/6	16 (7)	7.6 (1.5)
	4.6	6/6	40 (11)	4.5 (1.8)
	6.0	6/6	80 (16)	3.3 (0.6)
			ED_{50} = 4.6 (3.4–6.2) mg/kg§	

*The training of animals to discriminate (−)ephedrine from saline vehicle was recently reported; that study included a complete dose–response investigation of (−)ephedrine and a determination of its ED_{50} dose (19). The ED_{50} dose is reported here for comparison.
†*n*: number of animals responding/number of animals administered drug.
‡Data obtained during a 2.5 min extinction session; data are followed by ±SEM in parenthesis.
§ED_{50} value followed by 95% confidence limits.

drine from vehicle (19). Although the (+)amphetamine stimulus failed to generalize to (±)norephedrine (Table 1), data in Table 2 show that the (−)ephedrine stimulus did generalize to (±)norephedrine. The potency of (±)norephedrine (ED_{50} = 4.6 mg/kg) was found to be intermediate between that which we previously reported for (−)norephedrine and (+)norephedrine (ED_{50} doses = 1.9 and 5.8 mg/kg, respectively) in the (−)ephedrine-trained animals (19).

In summary, we have demonstrated that only two of the eight phenylpropanolamine isomers, (−)ephedrine and (+)cathine, produce amphetamine-like stimulus effects under the conditions employed. Both agents have been reported to produce amphetamine-like locomotor stimulation in rodents; they were the two most potent phenylpropanolamines, and their potencies differed only by a factor of two (4). With respect to potency in the (+)amphetamine-trained animals, (+)cathine is about half as potent as (−)ephedrine and, as we have previously reported, (−)ephedrine is about one-tenth as potent as (+)amphetamine. The present results stand in contrast to those obtained with the same agents using (−)ephedrine as the training drug. In the latter study it was demonstrated that six of the phenylpropanolamines produce (−)ephedrine-like effects. Furthermore, whereas the (+)amphetamine stimulus failed to generalize to (±)norephedrine, the (−)ephedrine stimulus did. It would appear, then, that the use of (−)ephedrine as a training drug cannot serve as a (+)amphetamine surrogate for predicting amphetamine-like effects. To this extent, these data confirm a premise raised by our prior investigation (20) that the 4 mg/kg-(−)ephedrine stimulus and 1 mg/kg-(+)amphetamine stimulus, although similar, are also quite different. However, because training dose and presession injection intervals can influence the outcome of drug discrimination studies (18), it remains to be determined whether the observed results are actual drug-related phenomena or whether they are dependent, at least to some extent, upon the training and testing parameters that were employed in the present study.

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