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Discriminative Stimulus Properties of (−)Ephedrine

RICHARD YOUNG AND RICHARD A. GLENNON

*Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia Campus, Virginia
Commonwealth University, Richmond, VA 23298-0540*

YOUNG, R. AND R. A. GLENNON. *Discriminative stimulus properties of (−)ephedrine.* PHARMACOL BIOCHEM BEHAV **60**(3) 771–775, 1998.—Ephedrine, a structural analog of methamphetamine, is one of the major constituents of legally available herbal dietary supplements. Although racemic ephedrine and ephedra extract have been previously used as training drugs in drug discrimination studies, there is evidence that the two optical isomers of ephedrine do not produce identical amphetamine-like stimulus effects in rats. Consequently, we trained a group of six male Sprague–Dawley rats to discriminate 4 mg/kg of the more potent optical isomer of ephedrine, (−)ephedrine, from saline vehicle. The (−)ephedrine stimulus ($ED_{50} = 0.8$ mg/kg) generalized to other central stimulants such as $S(+)$amphetamine ($ED_{50} = 0.4$ mg/kg), cocaine ($ED_{50} = 2.7$ mg/kg), methylphenidate ($ED_{50} = 1.2$ mg/kg), $S(−)$methcathinone ($ED_{50} = 0.3$ mg/kg), and caffeine ($ED_{50} = 36.7$ mg/kg), but stimulus generalization failed to occur to either $S(+)$methamphetamine or *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA). In addition, although we have previously shown that a (+)amphetamine stimulus generalizes to (−)ephedrine but not to (+)ephedrine, in the present investigation the (−)ephedrine stimulus generalized to (+)ephedrine ($ED_{50} = 2.6$ mg/kg). From the findings (a) that (−)ephedrine is approximately 10 times less potent than (+)amphetamine in (+)amphetamine-trained rats, whereas it is only half as potent as (+)amphetamine in (−)ephedrine-trained animals; (b) that the (−)ephedrine stimulus failed to generalize to (+)methamphetamine; and (c) that the (−)ephedrine stimulus generalized to (+)ephedrine, it is concluded that the stimulus effects of (+)amphetamine and (−)ephedrine as training drugs, while similar, are not identical. It is also concluded that the stimulus effects of (−)ephedrine and those of the designer drug MDMA, while perhaps sharing some amphetaminergic commonality, are nonidentical.   © 1998 Elsevier Science Inc.

Amphetamine   Ephedrine   Methamphetamine   Cocaine   Methylphenidate   Caffeine   MDMA
Methcathinone   Designer drugs   Herbal dietary supplements

EPHEDRA or ma huang typically refers to the entire aboveground portion of the plant *Ephedra sinica*. The plant has been used by the Chinese for several thousand years both for its medicinal qualities as an antiasthmatic and central stimulant (13), and as an intoxicant (14). Its principle pharmacologically active constituent, (−)ephedrine (13), is still in use today. Ephedrine is both an α- and β-adrenergic agonist and an agent that releases norepinephrine from sympathetic neurons (10). Ephedrine is also considered to be a potent central stimulant (10); however, its mechanism of action as a stimulant has not been well investigated.

The 1970s witnessed the emergence on the clandestine market of "look-alike drugs" and, in particular, of look-alike amphetamine or pseudospeed, which was deliberately manufactured to resemble amphetamine both in physical appearance and pharmacological effect (14–16). Typical amphetamine look-alikes contained caffeine (37–323 mg), ephedrine (12.5–50 mg), and/or norephedrine (phenylpropanolamine) (25–50 mg) (17). Ephedrine and norephedrine are β-hydroxy analogs of methamphetamine and amphetamine, respectively. β-Hydroxylation of amphetaminergic agents should reduce their lipophilicity and, hence, decrease their ability to penetrate the blood–brain barrier; consequently, this would result in agents with decreased central activity. Indeed, amphetamine has been demonstrated to be much more lipophilic than its β-hydroxylated derivatives (18) and, as central stimulants, it is generally concluded that the rank order of potency is amphetamine > ephedrine > norephedrine [reviewed in

(14)]. For example, in rats, (−)ephedrine is about 25-fold less potent than $S(+)$amphetamine as a locomotor stimulant; (+)ephedrine is even less active than its (−)enantiomer (2).

Although look-alike drugs are not as prevalent as they were a decade ago, with the 1990s has come the availability of herbal dietary supplements such as, for example, Herbal Ecstacy® (sic) (Global World Media Corp., Venice, CA) and Herbal XTC® (GH Applied Technologies Inc., Fairfield, CT). In addition to caffeine, both contain ephedrine in the form of ma huang. The amount of ma huang (or ephedrine) is not specified on the packaging for Herbal Ecstacy.® However Herbal XTC® contains 200 mg of ma huang per tablet and, according to the labeling, this represents approximately 18 mg of ephedrine. A companion product, Herbal XTC Enhancer® contains 590 mg of ma huang extract (providing 59 mg of ephedrine) per tablet.

Despite the widespread use of these herbal products (according to the lay press (1), manufacturers of Herbal Ecstacy® alone claim to have sold 150 million dose units), relatively little is known about the stimulus effects of ephedrine. Huang and Ho (12) demonstrated that racemic ephedrine produces >80% (+)amphetamine-appropriate responding in tests of stimulus generalization using (+)amphetamine-trained rats, whereas a subsequent study by Holloway et al. (11) reported a maximum of about 70% (+)amphetamine-appropriate responding. Racemic ephedrine (10 mg/kg)(5) and crude ephedra plant extract (4) have been used as training drugs in rats. The (±)ephedrine stimulus generalized to (±)amphetamine and cocaine (5), and the ephedra-extract stimulus generalized to $S(+)$methamphetamine (4). There is, then, evidence for some similarity between the stimulus effects produced by racemic ephedrine and amphetaminergic stimulants. However, Young et al. (20) recently have shown that whereas an $S(+)$amphetamine stimulus ($ED_{50} = 0.4$ mg/kg) generalizes to (−)ephedrine ($ED_{50} = 4.5$ mg/kg), it only partially generalizes to (+)ephedrine (maximum drug-appropriate responding = 50% at 12 mg/kg). So, although ephedrine has been previously used as a training drug (5), racemic ephedrine, not the more centrally active optical isomer, (−)ephedrine, was employed. The purpose of this present investigation was to determine if (−)ephedrine would serve as a training drug in animals and, if so, to examine several central stimulants in tests of stimulus generalization so as to better characterize the stimulus properties of this agent.

METHOD

Six male Sprague–Dawley rats, weighing 350–400 g at the beginning of the study, were used as subjects. The animals 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 4.0 mg/kg of (−)ephedrine 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 similar to that used to train rats to discriminate $S(+)$amphetamine from vehicle as previously described in detail (8). Briefly, daily training sessions were conducted with (−)ephedrine 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 half of the animals, the left lever was designated the drug-appropriate lever, whereas the situation was reversed for the remaining animals. Data collected during the extinction session included responses per minute (i.e., response rate) and number of responses on the drug-appropriate lever (expressed as a percent of total responses). Animals were not used in the stimulus generalization studies until they made greater 80% of their responses on the drug-appropriate lever after administration of (−)ephedrine, and less than 20% of their responses on the same drug-appropriate lever after administration of saline, for 3 consecutive weeks.

Tests of stimulus generalization were conducted to determine if the (−)ephedrine stimulus would generalize to the following agents (doses in parenthesis): (+)ephedrine (1.0, 2.0, 4.0, 8.0 mg/kg), $S(+)$amphetamine (0.25, 0.5, 0.75 mg/kg), methylphenidate (0.75, 1.25, 1.5 mg/kg), cocaine (2.0, 3.0, 3.5, 4.0 mg/kg), caffeine (3.0, 6.0, 12.0, 18.0, 24.0, 30.0, 40.0, 50.0 mg/kg), $S(−)$methcathinone (0.1, 0.25, 0.4, 0.5 mg/kg), $S(+)$methamphetamine (0.1, 0.3, 0.35, 0.4, 0.5 mg/kg), and MDMA (0.5, 1.0, 1.25, 1.5 mg/kg). During this phase of the study, maintenance of the (−)ephedrine-saline discrimination was insured 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, half of the animals would receive (−)ephedrine and 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, to groups of five to six 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 (−)ephedrine-appropriate lever. Animals making fewer than five total responses during the 2.5-min extinction session were considered as being disrupted. Where stimulus generalization occurred, ED_{50} values were calculated by the method of Finney (3). The ED_{50} doses are doses at which the animals would be expected to make 50% of their responses on the drug-appropriate lever.

Drugs

(−)Ephedrine hydrochloride ([1R,2S]-(−)-2[methylamino]-1-phenylpropan-1-ol HCl)*,* (+)ephedrine HCl ([1S,2R]-(+)-2-[methylamino]-1-phenylpropan-1-ol HCl), anhydrous caffeine, cocaine HCl, and $S(+)$amphetamine sulfate were obtained from Sigma-Aldrich Corp (St. Louis, MO). Methylphenidate HCl was purchased from Research Biochemicals Incorporated (Natick, MA). $S(−)$Methcathinone HCl was prepared as reported (8) and $S(+)$methamphetamine HCl and N-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane HCl (MDMA) were synthesized in house and available from earlier investigations.

Solutions of all drugs were made fresh daily in 0.9% sterile saline and all agents were administered via intraperitoneal injection usually in a 1.0 ml/kg injection volume. Doses of caffeine ≥30 mg/kg were administered in a 2.0 ml/kg injection volume. All doses refer to the weight of the salt.

RESULTS

Six rats were successfully trained to discriminate 4.0 mg/kg of (−)ephedrine from saline vehicle. Once the animals were trained, their response rates were similar under training drug (9.7 ± 2.1 responses per min) and saline (9.9 ± 2.0 responses per min) conditions. Administration of lower doses of (−)ephedrine to the (−)ephedrine-trained animals (Fig. 1) resulted in decreased drug-appropriate responding (ED_{50} = 0.8 mg/kg, 95% CL = 0.4–1.6 mg/kg).

Tests of stimulus generalization were conducted with several agents to characterize the (−)ephedrine stimulus; stimulus generalization occurred in all but two instances. Agents examined included (+)ephedrine (Fig. 1) (ED_{50} = 2.6 mg/kg; 95% CL = 1.2–5.6 mg/kg), $S(+)$amphetamine (Fig. 1) (ED_{50} = 0.4 mg/kg; 95% CL = 0.3–0.6 mg/kg), methylphenidate (Fig. 2) (ED_{50} = 1.2 mg/kg, 95% CL = 0.8–1.6 mg/kg), cocaine (Fig. 2) (ED_{50} = 2.7 mg/kg; 95% CL = 2.0–3.5 mg/kg), caffeine (Fig. 2) (ED_{50} = 36.7 mg/kg; 95% CL = 27.9–48.2 mg/kg), and $S(−)$methcathinone (Fig. 2) (ED_{50} = 0.3 mg/kg; 95% CL = 0.2–0.4 mg/kg). The (−)ephedrine stimulus failed to generalize to $S(+)$methamphetamine (Table 1); doses of ≤0.3 mg/kg resulted in a maximum of 13% (−)ephedrine-appropriate responding and doses >0.3 mg/kg of $S(+)$methamphetamine produced disruption of responding. As shown in Table 1, the (−)ephedrine stimulus also failed to completely generalize to MDMA. A dose of 0.5 mg/kg of MDMA elicited saline-appropriate responding; doses of 1.0 and 1.25 mg/kg of MDMA produced 49 and 58% drug-appropriate responding, respectively, but the animals' response rates were depressed. Following administration of 1.5 mg/kg of MDMA, none of the six animals made ≥5 responses during the entire extinction session.

DISCUSSION

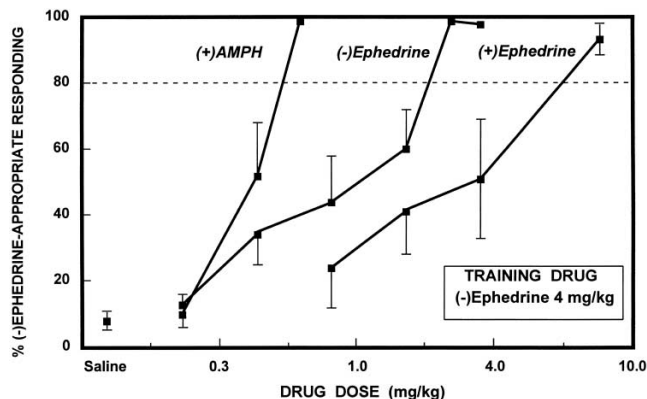(−)Ephedrine at a dose of 4.0 mg/kg serves as an effective training drug in rats. As such, this represents the first time animals have been trained to discriminate (−)ephedrine from vehicle. The (−)ephedrine stimulus (ED_{50} = 0.8 mg/kg) is dose dependent and administration of doses of (−)ephedrine lower than the training dose results in decreased (−)ephedrine-appropriate responding. Because (−)ephedrine is considered to be a central stimulant (10), we examined several other stimulants in tests of stimulus generalization. Figures 1 and 2 show that the (−)ephedrine stimulus generalizes to $S(+)$amphetamine, methylphenidate, $S(−)$methcathinone, and cocaine. We have previously demonstrated that an $S(+)$amphetamine stimulus generalizes to caffeine (20); in the present study, it is shown that the (−)ephedrine stimulus also generalizes to caffeine (Fig. 2). Furuya and Watanabe (4) have also found that caffeine substitutes in rats trained to ephedra extract.

The results to this point suggest that (−)ephedrine behaves essentially as expected—as an agent with central stimulant character. What is interesting is that we have previously shown that (−)ephedrine is 10-fold less potent than $S(+)$amphetamine in $S(+)$amphetamine-trained rats, whereas in the present investigation (−)ephedrine (ED_{50} = 0.8 mg/kg) is only about half as potent as $S(+)$amphetamine (ED_{50} = 0.4 mg/kg). It would appear that there might be some subtle differences between the stimulus properties of the two agents. Another indication that the (−)ephedrine and $S(+)$amphetamine stimulus are different is that the $S(+)$amphetamine stimulus only partially generalizes to (+)ephedrine (i.e., maximum of 50% $S(+)$amphetamine-appropriate responding; 12 mg/kg) (20), whereas the (−)ephedrine stimulus fully generalizes to (+)ephedrine (ED_{50} = 2.6 mg/kg).

Given that the (−)ephedrine stimulus generalizes to several central stimulants (Figs. 1 and 2), and in light of the report by Furuya and Watanabe (4) with animals trained to discriminate ephedra extract, it was expected that (−)ephedrine-stimulus generalization would also occur with $S(+)$methamphetamine. Table 1 shows, however, that stimulus generalization did not occur. $S(+)$Methamphetamine elicits saline-appropriate responding (i.e., a maximum of 13% drug-appropriate responding at 0.3 mg/kg) at the highest nondisruption dose evaluated; at this dose the animals' response rates were reduced by >50% compared to saline control rates. Doses of $S(+)$methamphetamine >0.3 mg/kg resulted in disruption of behavior. Variation of test parameters (e.g., examination of 0.4 mg/kg and 0.5 mg/kg of $S(+)$methamphetamine using a 5-min extinction session, or 0.35 mg/kg using a 30-min rather than the standard

FIG. 2. Effect (±SEM) of doses of $S(−)$methcathinone, methylphenidate, cocaine, and caffeine administered to rats trained to discriminate 4.0 mg/kg of (−)ephedrine from saline vehicle (n = 5–6 animals per each dose of each agent).
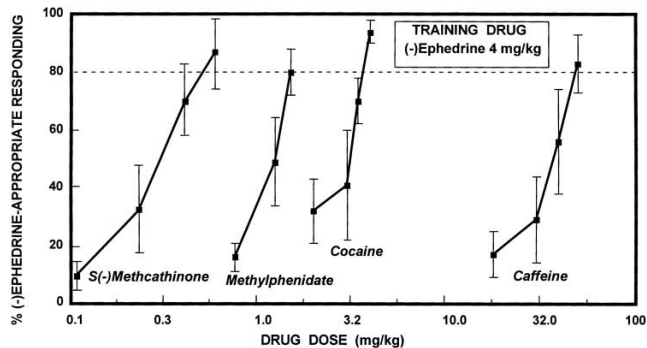

FIG. 1. Effect (±SEM) of doses of (+)amphetmine (AMPH), (−)ephedrine, and (+)ephedrine administered to rats trained to discriminate 4.0 mg/kg of (−)ephedrine from saline vehicle (n = 5–6 animals per each dose of each agent).

TABLE 1
AGENTS TO WHICH THE (−)EPHEDRINE STIMULUS FAILED TO GENERALIZE

Treatment	Dose (mg/kg)	n*	Drug-Appropriate Responding (±SEM)†	Response Rate; Responses/min (±SEM)†
(+) Methamphetamine	0.1	6/6	6% (±5)	14.4 (±4.3)
	0.3	5/6	13% (±6)	3.8 (±0.6)
	0.35	1/5	—‡	
	0.4	1/6	—‡	
	0.5	0/6	—‡	
MDMA	0.5	6/6	25% (±9)	10.1 (±4.3)
	1.0	4/6	49% (±22)	3.4 (±0.4)
	1.25	5/6	58% (±16)	6.6 (±1.9)
	1.50	0/6	—‡	
Saline 0.9%, 1 ml/kg		6/6	6% (±2)	9.9 (±2.0)

*n = Number of animals completing ≥5 responses during the extinction period/number of animals administered drug.
†Data collected during the 2.5-min extinction session.
‡Majority of animals failed to make ≥5 responses during the entire 2.5-min extinction session.

15-min presession injection interval) also resulted in disruption of behavior (data not shown). The present results stand in contrast to those of Furuya and Watanabe (4); however, because the ephedra plant is known to contain several ephedrine-related agents (13) it is possible that the presence of such agents in the extract could account for their findings. Because S(+)methamphetamine substitutes for S(+)amphetamine in S(+)amphetamine-trained animals (19), the lack of substitution in (−)ephedrine-trained animals represents yet another difference between the (−)ephedrine stimulus and the S(+)amphetamine stimulus.

Because ephedrine-containing herbal preparations are touted as legal alternatives to MDMA ("Ecstasy," "XTC") (1), it was of interest to determine if the (−)ephedrine stimulus would generalize to this designer drug. MDMA doses of 1.0 and 1.25 mg/kg resulted in partial generalization (Table 1); at these doses the animals' response rates were depressed. At 1.5 mg/kg, all six animals failed to respond. It might be noted that MDMA has been previously employed as a training drug in drug discrimination studies at doses ranging from 1.0 to 1.5 mg/kg (6); thus, doses used in the present study are reasonable for purposes of comparison. It would appear, then, that (−)ephedrine and MDMA are not producing identical stimulus effects at the doses evaluated. The fact that MDMA possesses some amphetaminergic character (6) likely accounts for the observed partial generalization.

The present investigation demonstrates that 4 mg/kg of (−)ephedrine serves as a training drug in rats, and that the (−)ephedrine stimulus substitutes for certain central stimulants: S(+)amphetamine, S(−)methcathinone, methylphenidate, cocaine, and caffeine. Interestingly, there are also some subtle differences between ephedrine and amphetaminergic agents. For example: (−)ephedrine seems more potent in (−)ephedrine-trained animals than it does in S(+)amphetamine-trained animals, the (−)ephedrine stimulus but not an S(+)amphetamine stimulus generalizes to (+)ephedrine, and an S(+)amphetamine but not the (−)ephedrine stimulus generalizes to S(+)methamphetamine. These results suggest that

(−)ephedrine and S(+)amphetamine share some similarities when employed as training drugs, but that the stimulus effects produced by these agents are not identical. The stimulus produced by S(+)amphetamine has been suggested to primarily involve a dopaminergic mechanism; nevertheless, there is some evidence for adrenergic involvement in the stimulus actions of this agent [reviewed (9,19)]. Ephedrine, in contrast, produces actions that seem to involve a significant adrenergic component (10). Although beyond the scope of the present investigation, future studies will focus on better defining the mechanism of action of (−)ephedrine as a discriminative stimulus. It is likely that differences in the stimulus actions of (−)ephedrine and S(+)amphetamine may be related to differences in the adrenergic/dopaminergic contributions to their mechanisms of action.

Finally, although certain herbal dietary supplements such as Herbal Ecstacy® and Herbal XTC® have been promoted as possible alternatives to the designer drug MDMA ("Ecstasy," "XTC"), it would seem on the basis of the present and previous (6) studies that MDMA and (−)ephedrine produce nonidentical stimulus effects but may share some amphetaminergic character. These results are consistent with the observation that administration of (−)ephedrine to MDMA-trained rats resulted in a maximum of 30% MDMA-appropriate responding (7). Nevertheless, because the herbal products also contain caffeine, it is perhaps premature to conclude that the herbal products are incapable of producing an MDMA-like effect; that is, similarity between the behavioral effects of MDMA and an ephedrine-caffeine combination has yet to be investigated. In any event, the amphetamine-like nature of ephedrine may be sufficient in itself to account, at least in part, for the abuse potential of ephedrine-containing products.

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