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Central stimulants as discriminative stimuli: Asymmetric generalization between (−)ephedrine and *S*(+)methamphetamine

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Abstract

Central stimulants readily serve as training stimuli in drug discrimination studies and typically substitute for one another in tests of stimulus generalization regardless of which is used as training drug. We have previously found that, although substitution occurs between (+)amphetamine and (−)ephedrine, substitution did not occur upon administration of *S*(+)methamphetamine to (−)ephedrine-trained animals. In the present investigation, rats were trained to discriminate *S*(+)methamphetamine (1 mg/kg) from saline vehicle and tests of stimulus generalization were performed with several stimulants, including (−)ephedrine. The *S*(+)methamphetamine stimulus (ED_{50} = 0.06 mg/kg) generalized to *R*(−)methamphetamine (ED_{50} = 1.61 mg/kg), *S*(+)amphetamine (ED_{50} = 0.28 mg/kg), *S*(−)methcathinone (ED_{50} = 0.21 mg/kg), methylphenidate (ED_{50} = 0.28 mg/kg), cocaine (ED_{50} = 3.68 mg/kg) and (−)ephedrine (ED_{50} = 13.1 mg/kg). Hence, stimulus generalization between *S*(+)methamphetamine and (−)ephedrine is apparently asymmetrical. In a companion study, *R*(−)methamphetamine was administered to rats trained to discriminate (−)ephedrine (4 mg/kg); substitution occurred and *R*(−)methamphetamine (ED_{50} = 0.92 mg/kg) was found to be nearly equipotent with (−)ephedrine (ED_{50} = 0.8 mg/kg). Although the exact basis for the observed results are unclear, they are discussed in terms of the different effects of (−)ephedrine and the methamphetamine optical isomers on neurotransmitter release and reuptake.

Keywords: *S*(+)Amphetamine; *S*(+)Methamphetamine; *R*(−)Methamphetamine; (−)Ephedrine; Cocaine; Methcathinone; Methylphenidate

1. Introduction

Central stimulants continue to represent a major drug abuse problem; examples of such stimulants include amphetamine, methamphetamine, methcathinone, (−)ephedrine, methylphenidate and cocaine. Of particular interest to the present investigation is (−)ephedrine—an "alternative psychoactive" that is a component of several herbal dietary supplements (e.g., Young et al., 1999). All of these agents have been the subject of investigations using drug discrimination studies. Although investigations are far from complete, where one of the agents has been used as training drug, the training stimulus typically generalizes to the other agents. For example, in *S*(+)amphetamine-trained animals, stimulus generalization was demonstrated to occur upon administration of each of the above agents (reviewed: Goudie, 1991; Kollins et al., 2001; Young and Glennon, 1986, 2000) and in cocaine-trained animals generalization occurred with (+)amphetamine, methamphetamine, methylphenidate (Woolverton, 1991) and methcathinone (Young and Glennon, 1993; Glennon et al., 1995). In *S*(−)methcathinone-trained animals, with the exception of ephedrine, which was not examined, stimulus generalization also occurred to each of the above agents (Young and Glennon, 1998a,b). This is not to say that these agents necessarily produce identical effects; however, these agents seemingly produce effects that are sufficiently similar to allow stimulus generalization to occur. The one rather curious exception is (−)ephedrine. With (−)ephedrine as training drug, dose-dependent stimulus generalization occurred to each of the above agents with the exception of *S*(+)methamphetamine. The latter agent produced a maximum of 13% (−)ephedrine-appropriate responding (at 0.3 mg/kg); *S*(+)methamphetamine doses ≥0.35 mg/kg disrupted the animals' ability to respond

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(Young and Glennon, 1998b). On the other hand, it has been only in recent years that methamphetamine has received attention as a training drug with rats (Ando and Yanagita, 1992; Miller et al., 2001; Munzar and Goldberg, 1999, 2000; Munzar et al., 1998, 1999a,b; Suzuki et al., 1997), mice (Witkin et al., 1999), pigeons (Li and McMillan, 1998; Sasaki et al., 1995), monkeys (Tidey and Bergman, 1998) and humans (Hart et al., 2000) as test subjects. The most common training dose of *S*(+)methamphetamine in rats is 1.0 mg/kg. (−)Ephedrine has been examined only once in methamphetamine-trained animals, but the rats were trained to discriminate racemic methamphetamine (0.5 mg/kg) from vehicle; (−)ephedrine was administered subcutaneously using a cumulative dosing procedure and, under these conditions, a cumulative dose of 32 mg/kg of (−)ephedrine engendered a maximum of about 78% drug-appropriate responding (Ando and Yanagita, 1992).

The present study was undertaken to evaluate the question: will *S*(+)methamphetamine-trained animals recognize (−)ephedrine? To this end, a group of rats was trained to discriminate *S*(+)methamphetamine from saline vehicle and tests of stimulus generalization were conducted with (−)ephedrine. *S*(+)Amphetamine, *S*(−)methcathinone, methylphenidate and cocaine were also examined for purpose of comparison. In a companion study, a second group of animals was trained to discriminate the effect of (−)ephedrine from saline. These animals were used to determine if stimulus generalization would also fail to occur to the *R*(−)isomer of methamphetamine as it did to *S*(+)methamphetamine.

2. Methods

2.1. Drug discrimination studies

The subjects were 13 male Sprague–Dawley rats (Charles River Laboratories) weighing 250–300 g at the beginning of the study. The animals were trained to discriminate either 1.0 mg/kg of *S*(+)methamphetamine ($n=8$) or 4.0 mg/kg of (−)ephedrine ($n=5$) from 0.9% saline vehicle in a manner previously described for (−)ephedrine (Young and Glennon, 1998b). In brief, 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 by restricting the availability of food. During the entire course of the study, the animals' body weights were maintained at this reduced level by restriction of food intake; the animals were allowed drinking water ad lib in their home cages. The animals were trained (15-min training session) to discriminate intraperitoneal injections (15-min presession injection interval) of *S*(+)methamphetamine from saline vehicle (sterile 0.9% saline) under a variable interval 15-s schedule of reward (i.e., sweetened milk) using standard two-lever Coulbourn Instruments operant equipment as previously described (Young and Glennon, 1998b). Daily training sessions were conducted with either *S*(+)methamphetamine or (−)ephedrine versus 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. The left lever was designated the drug-appropriate lever for approximately half the animals, whereas the situation was reversed for the remaining animals. Data collected during the extinction session included response rate (i.e., responses per minute) and number of responses on the drug-appropriate lever (expressed as a percent of total responses). Animals were not used in the subsequent stimulus generalization studies until they consistently made >80% of their responses on the drug-appropriate lever after administration of *S*(+)methamphetamine and <20% of their responses on the same drug-appropriate lever after administration of saline.

Tests of stimulus generalization (i.e., substitution) were conducted in order to determine if the *S*(+)methamphetamine stimulus would generalize to *S*(+)amphetamine, *S*(−)methcathinone, (−)ephedrine, methylphenidate, *R*(−)methamphetamine and cocaine, and with (−)ephedrine to determine if generalization would occur to *R*(−)methamphetamine. During this phase of the study, maintenance of the training-drug/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 the animals would receive the training dose of training drug and the remainder 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 the training drug and <20% of total responses on the same lever after administration of saline) during the extinction session were excluded from the next 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 test drugs were administered in a random order, using a 15-min presession injection interval, to the groups of rats with the proviso that if a particular dose of drug resulted in behavioral disruption, only lower doses would be investigated in subsequent sessions. Stimulus generalization was considered to have occurred when the animals, after a given dose of drug, made ≥80% of their responses (group mean) on the training drug-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 (1952). The ED_{50} doses are doses at which the animals would be expected to make 50% of their responses on the drug-appropriate lever.

2.2. Drugs

Methylphenidate hydrochloride, cocaine hydrochloride and (−)ephedrine HCl were purchased from Sigma-Aldrich (St. Louis, MO) and *S*(−)methcathinone hydrochloride was obtained from the WHO. *R*(−)Methamphetamine hydrochloride and (+)amphetamine sulfate were available in our laboratories from previous investigations. Doses refer to the weight of the salt. All solutions were prepared fresh daily and intraperitoneal injections were made 15 min prior to testing.

3. Results

Eight animals were trained to discriminate 1.0 mg/kg of *S*(+)methamphetamine from saline vehicle. The animals' mean response rate (11.5 responses/min) following this dose of drug was not substantially different than that following administration of saline vehicle (12.9 responses/min) (Fig. 1). Administration of lower doses of training drug resulted in the animals making a reduced number of responses on the drug-appropriate lever (Fig. 1); the calculated ED_{50} dose for *S*(+)methamphetamine was 0.06 (95% CL = 0.02–0.22) mg/kg.

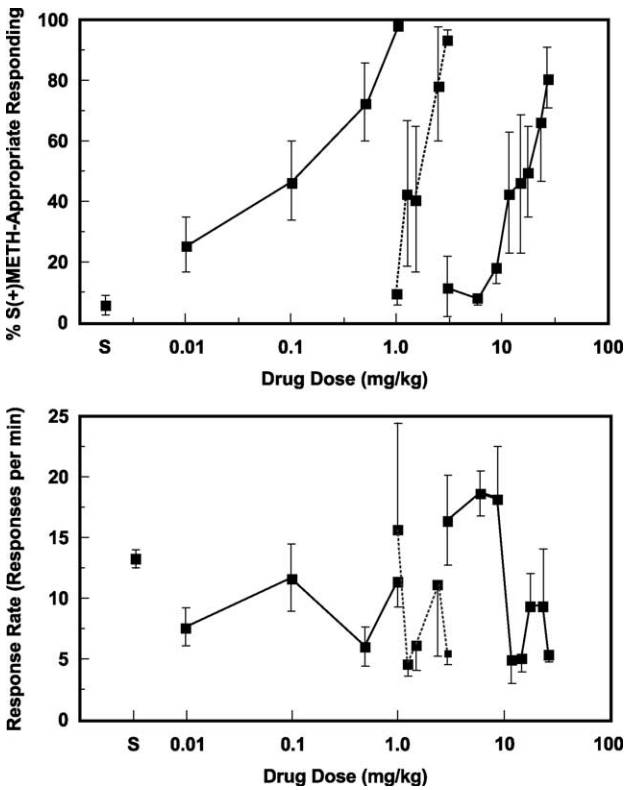

Fig. 1. Mean drug-appropriate responding (±S.E.M.) occasioned by animals trained to discriminate 1.0 mg/kg of *S*(+)methamphetamine from saline vehicle following administration of either *S*(+)methamphetamine (left), solid squares, *R*(−)methamphetamine (hatched line) or (−)ephedrine (right). S = effect of 1.0 ml/kg of 0.9% saline (upper panel). The animals' response rates (lower panel) reflect the responding of 8/8 animals for saline and (+)methamphetamine, and the responding of *n*/*n* animals (where *n*/*n* is the number of animals making ≥5 responses during the 2.5-min extinction session/number of animals administered drug) after administration of the following *R*(−)methamphetamine doses: 1.0 (5/5), 1.25 (4/4), 1.5 (5/5), 2.5 (3/4), 3.0 (4/5) or (−)ephedrine doses: 3.0 (6/6), 6.0 (6/6), 9.0 (6/6), 12 (4/5), 15 (4/5), 18 (5/5), 24 (5/5) and 27 (5/5) mg/kg.

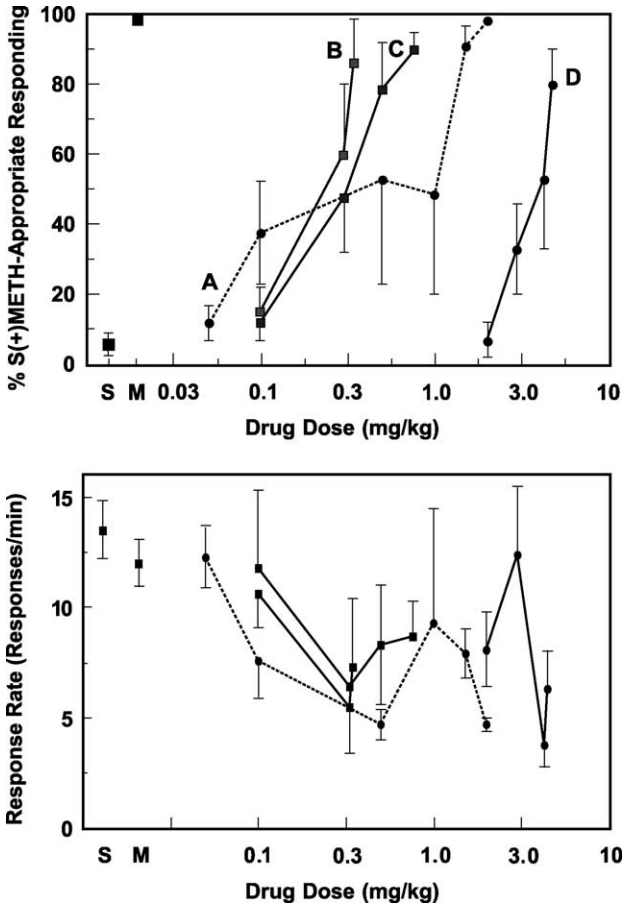

Fig. 2. Mean drug-appropriate responding (±S.E.M.) occasioned by animals trained to discriminate 1.0 mg/kg of *S*(+)methamphetamine from saline vehicle following administration of either methylphenidate (A), *S*(−)methcathinone (B), *S*(+)amphetamine (C) or cocaine (D). S = effect of 1.0 ml/kg of 0.9% saline; M = effect of the training dose of *S*(+)methamphetamine (upper panel). The animals' response rates (lower panel) reflect the responding of 8/8 animals for saline, (+)methamphetamine and (+)amphetamine; animals' response rates for the other agents represent the responding of *n*/*n* animals (where *n*/*n* is the number of animals making ≥5 responses during the 2.5-min extinction session/number of animals administered drug) for the following drugs doses: (−)methcathinone: 0.1 (6/6), 0.3 (5/6), 0.35 (3/5); methylphenidate: 0.05 (6/6), 0.1 (5/10), 0.5 (3/5), 1.0 (3/5), 1.5 (5/10), 2.0 (3/5); cocaine: 2.0 (4/4), 3.0 (5/5), 4.25 (4/5), 4.75 (4/5) mg/kg.

The *S*(+)methamphetamine stimulus generalized to each of the stimulants evaluated in this investigation (Figs. 1 and 2), and in each instance the animals' mean response rate at the drug dose that met generalization criteria was approximately 50% of the response rate following administration of 1.0 mg/kg of *S*(+)methamphetamine. Administration of eight doses of (−)ephedrine to the *S*(+)methamphetamine-trained animals resulted in a dose-related response pattern with 27 mg/

kg resulting in stimulus generalization (Fig. 1) (ED_{50} = 13.1 (95% CL = 9.0–19.2) mg/kg. Likewise, the following agents substituted for *S*(+)methamphetamine (followed by ED_{50} value and 95% CL in parenthesis): *R*(−)methamphetamine, 1.61 (1.12–2.31) mg/kg; *S*(+)amphetamine, 0.28 (0.16–0.49) mg/kg; *S*(−)methcathinone, 0.21 (0.11–0.40) mg/kg; methylphenidate, 0.28 (0.08–0.96) mg/kg; cocaine, 3.68 (2.71–4.99) mg/kg. Dose–response curves are shown in Figs. 1 and 2. Methcathinone doses of 0.4 and 0.5 mg/kg disrupted the animals' lever-pressing behavior and only two of five animals made ≥5 responses during the 2.5-min extinction session.

Five animals were trained to discriminate (−)ephedrine from vehicle; administered the training dose of the training drug, the animals made 98(±1)% of their responses on the (−)ephedrine-appropriate lever (response rate = 9.8 responses/min) (Fig. 3). Saline produced 6% drug-appropriate responding with a comparable response rate. Four doses of *R*(−)methamphetamine were examined and the (−)ephedrine stimulus generalized to *R*(−)methamphetamine in a dose-dependent manner (Fig. 3) (ED_{50} = 0.92 (95% CL = 0.54–1.57) mg/kg). The animals' response rates were comparable to the control response rate except that following 1.5 mg/kg of *R*(−)methamphetamine the animals' response rate (4.8 responses/min) was reduced by nearly 50%.

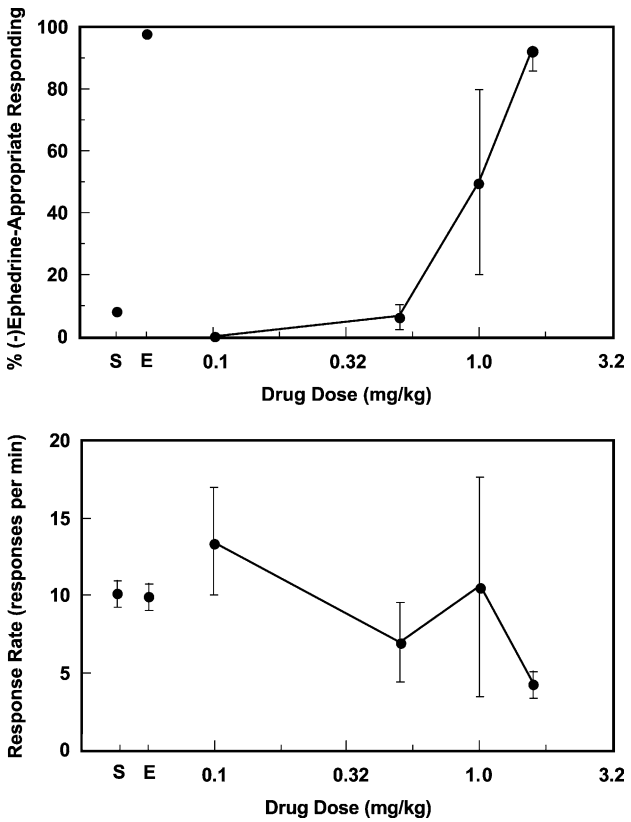

Fig. 3. Mean drug-appropriate responding (±S.E.M.) occasioned by animals trained to discriminate 4.0 mg/kg of (−)ephedrine from saline vehicle following administration of *R*(−)methamphetamine (upper panel). S = effect of 1.0 ml/kg of 0.9% saline; E = effect of the training dose of (−)ephedrine. The animals' response rates (lower panel) reflect the responding of 5/5 animals for (−)ephedrine and saline, and the responding of *n*/*n* animals (where *n*/*n* is the number of animals making ≥5 responses during the 2.5-min extinction session/number of animals administered drug) after administration of the following *R*(−)methamphetamine doses: 0.1 (5/5), 0.5 (5/5), 1.0 (4/5), 1.5 (4/5).

4. Discussion

Surprisingly, little has been published using rats trained to discriminate *S*(+)methamphetamine from vehicle; consequently, it was difficult to make many comparisons with previous reports. Sasaki et al. (1995), using pigeons trained to discriminate, presumably, racemic methamphetamine demonstrated substitution to amphetamine; methamphetamine was about twice as potent as amphetamine in that investigation. In general agreement with these results, *S*(+)methamphetamine was about four times more potent than *S*(+)amphetamine in the present investigation. Cocaine has been examined in pigeons (Sasaki et al., 1995; Li and McMillan, 1998), monkeys (Tidey and Bergman, 1998) and rats (Munzar and Goldberg, 2000) trained to discriminate either racemic or *S*(+)methamphetamine from vehicle; substitution occurred in each instance. In rats trained to discriminate 1.0 mg/kg of *S*(+)methamphetamine from vehicle, cocaine substituted for the training stimulus with an ED_{50} = 3.93 mg/kg (Munzar and Goldberg, 2000). The potency of cocaine in the present study (ED_{50} = 3.68 mg/kg) is nearly identical to that previously reported. The *S*(+)methamphetamine stimulus also generalized to *S*(−)methcathinone and methylphenidate (ED_{50} = 0.21 and 0.28 mg/kg, respectively). Although a (−)ephedrine stimulus failed to generalize to *S*(+)methamphetamine (Young and Glennon, 1998b), (−)ephedrine (ED_{50} = 13.1 mg/kg) substituted for *S*(+)methamphetamine (Fig. 1). Thus, these latter results, obtained from the particular training doses described above for *S*(+)methamphetamine and (−)ephedrine, indicate that asymmetric generalization occurs between these two agents. Moreover, it seems that (−)ephedrine stimulus generalization to methamphetamine occurred in a stereospecific manner. That is, (−)ephedrine-like responding was produced by *R*(−)methamphetamine (Fig. 3) but not by *S*(+)methamphetamine (Young and Glennon, 1998b).

Each of the stimulants was recognized by the *S*(+)methamphetamine-trained animals. Table 1 provides an overall summary of the relative potencies of the stimulants in animals trained to discriminate either *S*(+)methamphetamine, *S*(+)amphetamine, *S*(−)methcathinone or (−)ephedrine from saline vehicle. These results are from our laboratories and, hence, are consistent with respect to species, training and testing conditions, and equipment. Examination of the table reveals that cross-generalization is a common phenomenon amongst most of the agents and that ED_{50} values are also quite consistent. Two apparent inconsistencies are that (a) *S*(+)methamphetamine failed to substitute in (−)ephedrine

Table 1
Summary of stimulus generalization studies employing several different stimulants as training drug

Test drug	ED_{50} dose (mg/kg)			
	Training drug			
	S(+) METH[a]	*S*(+) AMPH[b]	*S*(−) Methcathinone[c]	(−) Ephedrine[d]
S(+)Methamph	0.06	0.20	0.17	NG[e]
S(−)Methcath	0.21	0.18	0.11	0.3
S(+)AMPH	0.28	0.44	0.23	0.4
Methylphenidate	0.28	[f]	0.83	1.2
(−)Ephedrine	13.1	4.5	[f]	0.8
Cocaine	3.68	5.63	1.47	2.7

[a] Results from the present investigation.
[b] Data from Young and Glennon (1986, 2000).
[c] Data from Young and Glennon (1998a).
[d] Data from Young and Glennon (1998b).
[e] Stimulus generalization did not occur; see Section 1.
[f] Agent not tested.

trained animals and (b) although (−)ephedrine substituted in *S*(+)methamphetamine-trained animals, it was substantially less potent than the training drug. Taken alone, the latter point might not be unusual and could be explained, at least in part, by a difference in the pharmacokinetics of the two agents. That is, ephedrine is a β-hydroxy analog of methamphetamine and is thought to be less lipophilic and, hence, less able to penetrate the blood–brain barrier (Vree et al., 1969). Consequently, it might be expected that ephedrine would be a less potent central stimulant than methamphetamine. However, when taken together, there appears to be something unique between this pair of agents. Perhaps an explanation might be found with their mechanisms of action but, unfortunately, the exact neurochemical mechanisms of action of these two agents as training drugs have yet to be fully elucidated.

S(+)Methamphetamine is thought to produce its stimulus effects primarily via release of dopamine (Munzar et al., 1999a). Blockade of dopamine reuptake contributes to its actions, and release of norepinephrine, blockade of norepinephrine reuptake, and possibly direct interaction with pre- and postsynaptic α_2-adrenergic receptors also have contributing or modulatory roles (Munzar and Goldberg, 2000; Tidey and Bergman, 1998). Support for dopaminergic involvement is based on the findings that dopamine reuptake inhibitors, D1 receptor agonists and D2 receptor agonists, substitute for methamphetamine and that the methamphetamine stimulus is antagonized by nonselective D1/D2 antagonists, a combination of a D1 plus a D2 antagonist, and both by D1- and D2-selective antagonists (Munzar and Goldberg, 2000; Tidey and Bergman, 1998). Other evidence suggests additional modulatory roles for serotonergic (Munzar et al., 1999a,b; Tidey and Bergman, 1998) and histaminergic systems (Munzar et al., 1998). (−)Ephedrine is at least 50 times less potent than *S*(+)methamphetamine as a dopamine releasing agent (Rothman et al., 2001), and is also much less potent than *S*(+)methamphetamine as an inhibitor of dopamine reuptake. Because (−)ephedrine is 20 times more potent as a norepinephrine releasing agent and reuptake inhibitor than it is at producing the corresponding dopaminergic actions, its adrenergic actions might predominate (relative to its dopaminergic actions) when (−)ephedrine is used as a test drug or as a training drug. That is, even though (−)ephedrine might act on both neurotransmitter systems, animals trained to (−)ephedrine might focus primarily on its greater adrenergic character. The potencies of *S*(+)methamphetamine and *S*(+)amphetamine to release norepinephrine or dopamine, or to block norepinephrine or dopamine reuptake, are relatively similar (Rothman et al., 2001). It is unlikely, then, that one of these mechanisms can account for the ability of the (−)ephedrine stimulus to generalize to *S*(+)amphetamine but not *S*(+)methamphetamine (Young and Glennon, 1998b). Nevertheless, the low potency of (−)ephedrine in *S*(+)methamphetamine-trained animals could be explained by its low potency in dopaminergic release and reuptake assays. Although additional studies with (−)ephedrine-trained animals will be required to further determine the relative roles of norepinephrine versus dopaminergic actions, and although the direct interaction of (−)ephedrine at adrenergic receptors can not be excluded at this time, the above mentioned concept can be evaluated. *R*(−)Methamphetamine, unlike its optical isomer, has a greater effect on norepinephrine release and reuptake than on dopamine release and reuptake, respectively (Rothman et al., 2001). In fact, the potency of *R*(−)methamphetamine on norepinephrine and dopamine release and reuptake is a close match to (−)ephedrine. It might be expected, then, that there would be good likelihood for the (−)ephedrine stimulus to generalize to *R*(−)methamphetamine even though the (−)ephedrine stimulus did not generalize to *S*(+)methamphetamine. Indeed, this was found to be the case and the potencies of (−)ephedrine (ED_{50} = 0.8 mg/kg) (Young and Glennon, 1998b) and *R*(−)methamphetamine (ED_{50} = 0.92 mg/kg) to produce (−)ephedrine-like stimulus effects were nearly identical.

R(−)Methamphetamine is about 18-fold less potent than *S*(+)methamphetamine as a dopamine-releasing agent, and 40-fold less potent as a dopamine reuptake inhibitor (Rothman et al., 2001). It might also be noted (present investigation) that *R*(−)methamphetamine was 25-fold less potent than its opposite enantiomer in *S*(+)methamphetamine-trained animals. It is quite possible that a combination of noradrenergic character together with reduced dopaminergic character accounts for the similarities between the stimulus effects of *R*(−)methamphetamine and (−)ephedrine. The enhanced dopaminergic character of *S*(+)methamphetamine might account for the observations that (i) its administration to (−)ephedrine-trained animals resulted in behavioral disruption and that (ii) (−)ephedrine displayed low potency upon administration to *S*(+)methamphetamine-trained animals.

Each of the stimulants examined produced *S*(+)methamphetamine-like stimulus effects in rats. In general, these findings are not unanticipated given what has been previously reported with various other training drugs (see Section 1 and data in Table 1). Nevertheless, it is curious that (−)ephedrine produced *S*(+)methamphetamine-like stimulus effects with low potency relative to either the training dose of *S*(+)methamphetamine, or to its potency in (−)ephedrine-trained animals (Table 1). Each of the stimulants in the present investigation has a pronounced influence on dopaminergic and noradrenergic systems. Roles for one or both of these systems have been suggested as underlying their stimulus effects in animals (for example, Ando and Yanagita, 1992; Goudie, 1991; Kollins et al., 2001; Munzar and Goldberg, 2000; Sasaki et al., 1995; Tidey and Bergman, 1998; Woolverton, 1991; Young and Glennon, 1998a,b, 2000). However, these agents do not necessarily influence dopaminergic and noradrenergic systems in exactly the same manner (i.e., direct versus indirect action, release versus inhibition of reuptake) or with the same potency. Stimulus similarities might be attributed to the overall effect of the stimulants on these neurotransmitter systems, but observed inconsistencies (i.e., lack of (−)ephedrine-stimulus generalization to *S*(+)methamphetamine, low potency of (−)ephedrine in *S*(+)methamphetamine-trained animals) might be attributed to subtle differences in their neurochemical interactions.

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