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Discriminative stimulus properties of α-ethyltryptamine optical isomers☆

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Abstract

α-Ethyltryptamine (α-ET) possesses central stimulant and hallucinogenic activity. Also, in tests of stimulus generalization using rats trained to discriminate the controlled substance analog (i.e., designer drug) *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA) from vehicle, α-ET substituted for MDMA. These previous studies employed racemic α-ET. Because psychoactive phenylalkylamines with abuse potential can produce one or more of three distinct stimulus effects (i.e., amphetamine-, DOM- and/or PMMA-like effects) in animals trained to discriminate either the stimulant (+)amphetamine, the hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), or *N*-methyl-1-(4-methoxyphenyl)-2-aminopropane (PMMA) from vehicle, and because these effects can be stereoselective, the individual optical isomers of α-ET were examined in groups of animals trained to discriminate (+)amphetamine, DOM, PMMA and MDMA from saline vehicle. (−)α-ET (ED_{50} = 7.8 mg/kg), but not (+)α-ET (maximum of 53% drug-appropriate responding), substituted for (+)amphetamine, whereas (+)α-ET (ED_{50} = 2.7 mg/kg), but not (−)α-ET (maximum of 33% drug-appropriate responding), substituted for DOM. Both optical isomers of α-ET substituted for PMMA and MDMA with ED_{50} values of 1.6 and 1.4 mg/kg (PMMA-trained animals) and 1.3 and 2.0 mg/kg (MDMA-trained animals) for (−)α-ET and (+)α-ET, respectively. The results of this investigation suggest that both optical isomers of α-ET are capable of producing an MDMA/PMMA-like effect at nearly comparable doses, and that the stimulant or amphetamine-like nature of α-ET resides primarily with its (−)isomer whereas hallucinogenic or DOM-like character resides primarily with the (+)enantiomer.

Keywords: Stimulants; Hallucinogens; Designer drugs; MDMA; Amphetamine; PMMA

1. Introduction

α-Ethyltryptamine (etryptamine, α-ET, AET) was briefly employed as an antidepressant or psychic energizer (Monase) in the early 1960s[1] but was removed from the market shortly after its introduction. Structurally, α-ET is the α-ethyl homolog of the hallucinogen α-methyltryptamine (Murphree et al., 1961). Like α-methyltryptamine, α-ET has been shown to be hallucinogenic in humans (Murphree et al., 1961). α-ET also produces amphetamine-like locomotor stimulation (Hoffer and Osmond, 1967; Lessin et al., 1965). Consequently, it is commonly thought that α-ET is both a central stimulant and a hallucinogenic agent (Hoffer and Osmond, 1967). Consistent with these reports, we demonstrated that α-ET substitutes for DOM (i.e., 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane) in rats trained to discriminate this phenylalkylamine hallucinogen from vehicle in a two-lever drug discrimination paradigm (Glennon et al., 1983b). However, administration of α-ET to (+)amphetamine-trained rats resulted only in partial generalization (i.e., a maximum of 41% drug-appropriate responding) (Glennon, 1993).

In 1993, it was shown that α-ET also substitutes in rats trained to discriminate the phenylalkylamine empathogen *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (“Ecstasy,” “XTC,” “E,” “x” or MDMA) from vehicle (Glennon, 1993). More recently, Schechter (1998) confirmed this latter finding, and Krebs and Geyer have found

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[1] A supplement of the Journal of Neuropsychiatry (1961, 2, Supplement 1) was devoted almost entirely to the preclinical and clinical pharmacology of α-ET.

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that MDMA and α-ET have similar effects on unconditioned motor behavior in rats (Krebs and Geyer, 1993). While our work was in progress, we learned that α-ET had begun making an appearance on the street as a "designer drug" ("ET"; "Love Pearls") and that its effects were similar to those produced by MDMA (F. Sapienza, DEA; personal communication). Reportedly, α-ET is being sold on the illicit market as a substitute for MDMA (Martinez and Geyer, 1997).

Phenylalkylamines with abuse potential can produce one or more of at least three distinct stimulus effects in animals: a DOM-like or "hallucinogenic" effect, an amphetamine-like effect, and a third type of effect for which PMMA, or *N*-methyl-(4-methoxyphenyl)-2-aminopropane, has become an example (Glennon, 1999; Glennon et al., 1997; Rangisetty et al., 2001). Evidence suggests that the stimulus effects of DOM involve a 5-HT_{2A} agonist mechanism whereas the effects of (+)amphetamine seem primarily mediated via a catecholaminergic mechanism (Glennon, 1999). At this time, the mechanism of action of PMMA as a discriminative stimulus is unknown. Some agents are capable of producing more than one type of effect; for example, MDMA substitutes both for (+)amphetamine and for PMMA (Glennon, 1999; Rangisetty et al., 2001). Furthermore, the stimulus effects of phenylalkylamines can be stereoselective or stereospecific depending upon the agent being examined; that is, both optical isomers or perhaps only a single isomer will substitute. The desmethyl analog of MDMA (i.e., MDA or 1-(3,4-methylenedioxyphenyl)-2-aminopropane) is a case in point. *R*(−)MDA substitutes for DOM but not for (+)amphetamine, whereas *S*(+)MDA substitutes for (+)amphetamine but not for DOM (Young and Glennon, 1996). In fact, animals can be trained to discriminate *R*(−)MDA from *S*(+)MDA from vehicle in a three-lever discrimination task, and whereas administration of DOM engenders *R*(−)MDA-appropriate responding, (+)amphetamine elicits *S*(+)MDA-appropriate responding (Young and Glennon, 1996).

α-ET behaves as a hallucinogen, as a central stimulant, and substitutes for MDMA in MDMA-trained animals. However, previous studies were performed using racemic α-ET. In the present investigation, both optical isomers of α-ET were prepared and examined in groups of rats trained to discriminate one of four training drugs from vehicle: (+)amphetamine, DOM, PMMA and MDMA. It was thought that such an examination of the enantiomers might highlight any putative difference(s) in their action(s). For example, the possibility exists that amphetamine-like activity rests predominantly with one optical isomer of α-ET and that its opposite enantiomer adds little to, or perhaps even hinders, the occurrence of complete stimulus generalization. Consequently, this might explain why administration of racemic α-ET to (+)amphetamine-trained animals resulted only in 41% drug-appropriate responding (Glennon, 1993). Using this approach, it should be possible to determine which effect(s) is(are) related to which optical isomer.

2. Methods

2.1. Drug discrimination studies

The subjects, 20 male Sprague–Dawley rats (Charles River Laboratories) weighing 250–300 g at the beginning of the study, were trained to discriminate one of four different training drugs from saline vehicle. Animals were housed individually and, prior to the start of the study, caloric intake was restricted such that the animals' body weights were reduced to, and maintained at, approximately 80% of their free-feeding weight. Such caloric intake has been shown to lengthen lifespan and decrease the incidence of pathologies in the rat (Keenan et al., 1994). During the entire course of the study, the animals' body weights were maintained at this reduced level; drinking water was freely available in the animals' home cages. The rats were trained (15-min training session) to discriminate intraperitoneal injections (15-min presession injection interval) of (+)amphetamine (1.0 mg/kg), DOM (1.0 mg/kg), MDMA (1.5 mg/kg) or PMMA (1.25 mg/kg) from saline vehicle (sterile 0.9% saline) under a variable interval 15-s schedule of reward (i.e., sweetened milk) using standard (Coulbourn Instruments) two-lever operant equipment. We have previously reported the training of groups of animals to each of these four agents; see Rangisetty et al. (in press) for a discussion and for further detail. Daily training sessions were conducted with training drug 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 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; resp/min) 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 training drug, 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 various training drug stimuli would generalize to the optical isomers of α-ET. 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 one of the 2 days before a generalization test, approximately half of the animals would receive the training dose of the 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 training drug and <20% of total responses on the same lever after administration of saline)

Table 1
Results of substitution studies with optical isomers of α-ET in groups of animals trained to discriminate either (+)amphetamine, DOM, MDMA or PMMA from saline vehicle

Treatment	Dose (mg/kg)	N[a]	% Drug-appropriate responding (±S.E.M.)[b]	Response rate resp/min; (±S.E.M.)[b]
(+)Amphetamine-trained animals				
(−)α-ET	3.0	5/5	16 (7)	10.8 (1.5)
	6.0	5/5	35 (13)	6.9 (1.4)
	9.0	3/5	40 (4)	7.6 (4.4)
	12.0	3/5	81 (1)	5.6 (2.4)
			ED_{50} = 7.8 (3.8–16.0) mg/kg[c]	
(+)α-ET	2.0	5/5	21 (8)	11.5 (1.9)
	4.0	4/5	43 (7)	8.7 (3.4)
	5.0	3/5	53 (13)	6.3 (3.6)
	5.5	1/5	–[d]	
	6.0	0/5	–[d]	
(+)Amphetamine	1.0	5/5	95 (2)	8.7 (1.8)
Saline (1 ml/kg)		5/5	8 (4)	10.9 (2.3)
DOM-trained animals				
(−)α-ET	0.25	4/5	6 (5)	22.4 (8.7)
	0.5	4/5	21 (21)	32.6 (16.9)
	1.0	3/5	10 (10)	43.9 (16.9)
	2.0	3/5	33 (33)	12.0 (9.0)
	3.0	1/5	–	–
	4.0	0/5	–	–
(+)α-ET	2.0	5/5	20 (18)	18.4 (5.2)
	2.5	3/5	30 (30)	17.5 (7.0)
	3.0	3/5	57 (16)	7.4 (2.7)
	3.5	3/5	90 (7)	3.7 (1.0)
	4.0	1/5	–	–
			ED_{50} = 2.7 (2.1–3.5) mg/kg[c]	
DOM	1.0	5/5	98 (1)	21.4 (3.5)
Saline (1 ml/kg)		5/5	7 (3)	23.6 (5.1)
MDMA-trained animals				
(−)α-ET	0.5	5/5	19 (7)	12.0 (1.7)
	1.5	5/5	49 (17)	12.1 (1.0)
	3.0	5/5	73 (13)	11.5 (3.0)
	4.0	5/5	95 (2)	8.1 (1.0)
			ED_{50} = 1.3 (0.6–2.9) mg/kg[c]	
(+)α-ET	1.5	5/5	10 (4)	10.2 (1.9)
	2.0	5/5	48 (17)	9.7 (1.4)
	2.25	5/5	75 (7)	8.6 (1.4)
	3.0	5/5	93 (4)	11.4 (1.1)
			ED_{50} = 2.0 (1.6–2.5) mg/kg[c]	
MDMA	1.5	5/5	96 (3)	13.1 (3.6)
Saline (1 ml/kg)		5/5	8 (4)	13.9 (2.9)
PMMA-trained animals				
(−)α-ET	1.0	5/5	22 (11)	12.6 (3.5)
	2.0	3/5	62 (20)	14.5 (5.3)
	3.0	3/5	86 (7)	7.1 (2.8)
			ED_{50} = 1.6 (0.9–2.9) mg/kg[c]	
(+)α-ET	1.0	5/5	26 (7)	17.2 (2.9)
	1.5	5/5	50 (11)	10.5 (4.4)
	2.0	5/5	88 (10)	5.2 (1.6)
			ED_{50} = 1.4 (1.0–1.8) mg/kg[c]	
PMMA	1.25	5/5	97 (2)	12.4 (2.6)
Saline (1 ml/kg)		5/5	5 (2)	13.9 (3.1)

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 the test drugs were administered in a random order, using a 15-min presession injection interval, to groups of five rats. Stimulus generalization was considered to have occurred when the animals, after a given dose of drug, made $\geq$ 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

1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane hydrochloride (DOM) was a gift from NIDA and (+)amphetamine sulfate was available from earlier studies in our laboratory. MDMA and *N*-methyl-1-(4-methoxyphenyl)-2-aminopropane hydrochloride were synthesized in our laboratories. The optical isomers of α-ethyltryptamine acetate were prepared according to the published method of Anthony (Anthony, 1970); melting points and optical rotations were consistent with reported values.

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

Four groups of five rats were trained to discriminate either 1.0 mg/kg of (+)amphetamine, 1.0 mg/kg of DOM, 1.5 mg/kg of MDMA or 1.25 mg/kg of PMMA from vehicle. Once trained, the (+)amphetamine-, DOM-, MDMA- and PMMA-trained rats made $\geq$ 95% of their responses on the drug-appropriate lever when administered training drug, and < 10% of their responses on the same lever following administration of saline (Table 1). Response rates (mean

Notes to Table 1

[a] Number of animals completing at least five responses during the extinction period/number of animals administered drug.

[b] Data collected during a 2.5-min extinction session. Response rates reflect responding only of those animals making five or more responses during the extinction session.

[c] Effective dose 50 followed by 95% confidence limits.

[d] Disruption; majority of animals failed to make at least five responses during the entire extinction session.

responses/min) were not substantially different after training dose and saline treatments in each group of animals.

Doses of α-ET optical isomers were administered to each group of animals in tests of stimulus generalization (Fig. 1). The (+)amphetamine stimulus generalized to (−)α-ET (ED_{50} = 7.8 mg/kg) in a dose-related manner; a depressed response rate (≈40% reduction when compared to the response rate after administration of (+)amphetamine) was noted, however, at the (−)α-ET dose (12.0 mg/kg) that produced >80% amphetamine-appropriate responding. Administration of 2.0–5.0 mg/kg of (+)α-ET produced a maximum of 53% (+)amphetamine-appropriate responding; doses of 5.5 and 6.0 mg/kg resulted in behavioral disruption. The animals' response rates following the administration of 5.0 mg/kg of (+)α-ET was reduced by approximately 30% when compared to the response rate after administration of (+)amphetamine.

The DOM stimulus generalized to (+)-α-ET (ED_{50} = 2.7 mg/kg) in a dose-related fashion; this substitution, however, was accompanied by a >80% decrease in response rate when compared to the response rate following administration of DOM. Administration of 0.25–2.0 mg/kg of (−)α-ET resulted in a maximum of 33% DOM-appropriate responding; doses of 3.0 and 4.0 mg/kg of (−)α-ET disrupted the animals' behavior. The animals response rate following the administration of 2.0 mg/kg of (−)α-ET was decreased by >40% when compared to the response rate following the administration of DOM.

Both isomers of α-ET substituted for MDMA and there was less than a two-fold difference in potency. Potencies (ED_{50} values) calculated for (−)α-ET and (+)α-ET were 1.3 and 2.0 mg/kg, respectively. The animals' response rates were diminished by about 40% and 13% at the (−)α-ET dose (4.0 mg/kg) and the (+)α-ET dose (3.0 mg/kg), respectively, that produced >90% MDMA-appropriate responding, when compared to the respective rate following administration of MDMA.

As in the MDMA-trained animals, both isomers of α-ET substituted for PMMA. Here, too, the α-ET isomers were nearly equipotent with calculated ED_{50} values of 1.6 and 1.4 mg/kg for (−)α-ET and (+)α-ET, respectively. The animals' response rates were decreased by 43% and 59% at the (−)α-ET dose (3.0 mg/kg) and the (+)α-ET dose (2.0 mg/kg), respectively, that produced >80% drug-appropriate

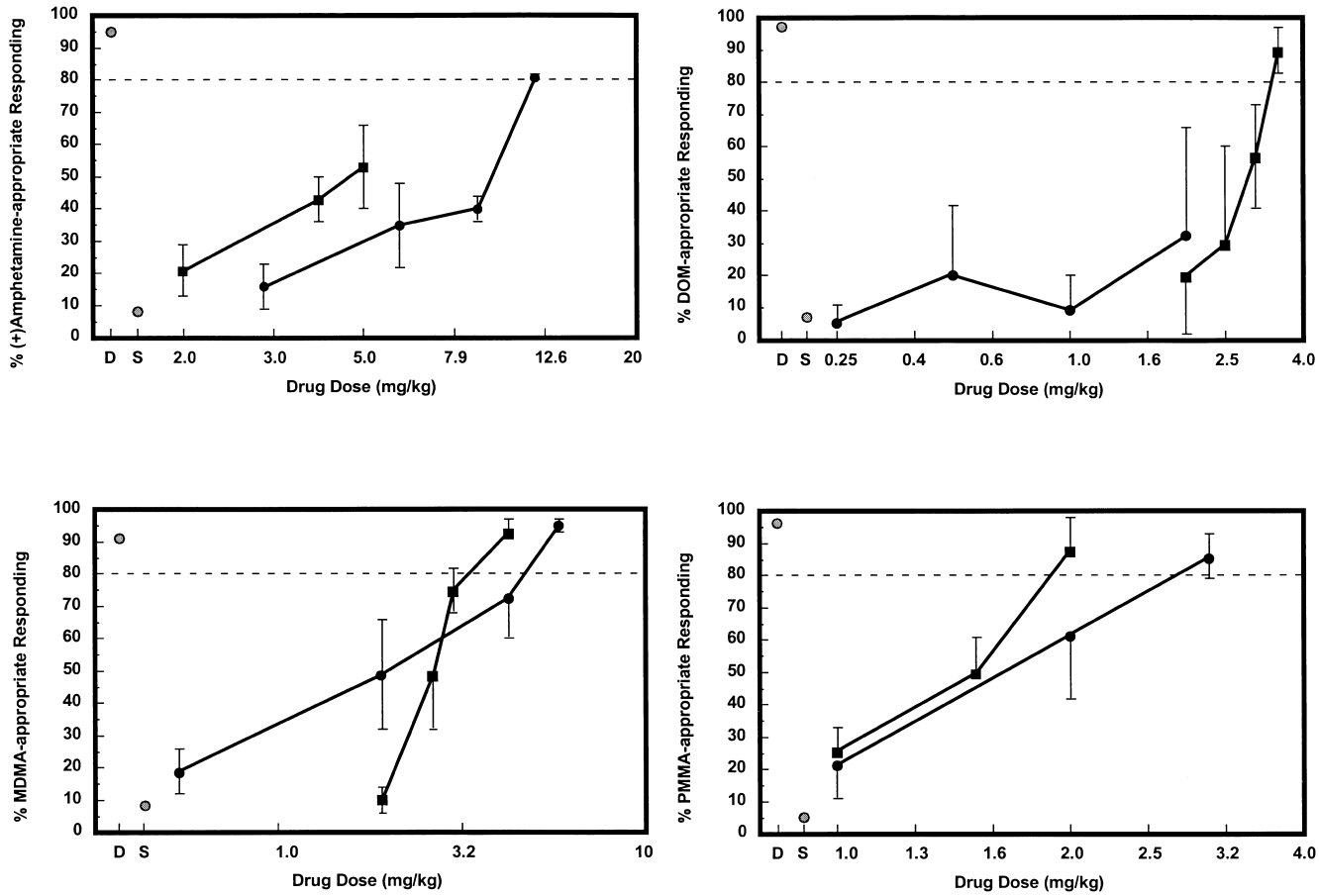

Fig. 1. Results of stimulus generalization studies with the optical isomers of α-ET in groups of rats trained to discriminate either (+)amphetamine (upper left panel), DOM (upper right panel), MDMA (lower left panel) or PMMA (lower right panel) from saline vehicle. In each case, the solid circles represent (−)α-ET and the solid squares represent (+)α-ET; D designates the effect of the training dose of the particular training drug, and S represent the effect of saline. Drug doses are plotted on a logarithmic scale. See Table 1 for the number of animals responding at each dose, and for the animals' mean response rates.

responding, when compared to the response rate following administration of PMMA.

4. Discussion

We have previously shown that stimulus generalization occurs upon administration of α-ET to DOM-trained animals (Glennon, 1993). In that study, the potency (ED_{50}) of racemic α-ET was calculated to be 6.6 mg/kg. The present investigation demonstrates that the DOM-like properties of α-ET reside primarily with its (+)isomer, and that (+)α-ET is approximately twice as potent as its racemate. For a related hallucinogen, 5-methoxy-α-methyltryptamine (5-OMe α-MeT), it was previously demonstrated that (+)5-OMe α-MeT is more potent than either (−)5-OMe α-MeT or its racemate in DOM-trained animals (Glennon et al., 1983a). Hence, from a stereochemical standpoint, the present results are consistent with the earlier finding for a structurally related agent.

Interestingly, the DOM stimulus did not generalize to (−)α-ET (Table 1). However, the (+)amphetamine stimulus did generalize to (−)α-ET but not to (+)α-ET (Table 1). These results are quite reminiscent of those obtained with MDA. That is, the DOM-like character of MDA is associated primarily, if not exclusively, with one isomer (i.e., *R*(−)MDA) whereas the amphetamine-like character is associated with the opposite optical isomer (Young and Glennon, 1996). From this perspective, α-ET might be viewed as a tryptamine counterpart of the phenylalkylamine MDA; (+)α-ET is the optical isomer with predominantly DOM character whereas (−)α-ET is the optical isomer with predominantly amphetamine character.

In addition to possessing DOM and amphetamine character, racemic MDA possesses MDMA character. That is, stimulus generalization occurred upon administration of MDA to MDMA-trained animals (Glennon et al., 1988). This action is not stereospecific in that both optical isomers of MDA substituted for MDMA (Glennon et al., 1988). We have previously demonstrated stimulus similarity between MDMA and racemic α-ET (Glennon, 1993). In the present investigation, it was found that both isomers of α-ET substitute for MDMA.

Because MDMA possesses both amphetaminergic and PMMA-like character (i.e., stimulus generalization occurs between MDMA and PMMA regardless of which is used as training drug, but only MDMA and not PMMA substitute for the amphetamine in (+)amphetamine trained animals) (Glennon et al., 1997; Rangisetty et al., 2001), it was of interest to determine whether or not either isomer of α-ET would substitute for PMMA. That is, although (−)α-ET substituted for MDMA, this might be the result of its amphetaminergic actions. This seems unlikely because (+)α-ET also substituted for MDMA. However, it could be argued that (+)α-ET possesses some amphetaminergic action, and that the reason complete (+)amphetamine stimulus generalization was not seen upon administration of (+)α-ET to (+)amphetamine trained animals is because its DOM-like actions disrupted the animals' behavior. Consequently, both isomers were examined in PMMA-trained animals. Both isomers substituted for PMMA. Clearly, there is some similarity between the stimulus effects produced by PMMA, (+)α-ET, and (−)α-ET.

The results of the present study lend support to the concept that α-ET is a central stimulant that can produce hallucinogenic and, according to anecdotal evidence, MDMA-like effects in humans. It has already been shown that racemic α-ET substitutes for DOM and MDMA. In the present investigation, it is shown that administration of (−)α-ET but not (+)α-ET results in stimulus generalization when administered to (+)amphetamine-trained rats and that (+)α-ET but not (−)α-ET results in generalization when administered to DOM-trained animals. Both optical isomers also substituted for MDMA and PMMA. As such, α-ET is the first tryptamine or indolealkylamine derivative to display all three types of stimulus effects (i.e., amphetamine-, DOM- and MDMA/PMMA-like). It might be this combination of effects that makes α-ET a unique and attractive drug of abuse.

The present findings are also of interest from a theoretical perspective. Numerous agents result in partial generalization when administered to animals trained to discriminate a given training drug from vehicle; it is difficult to draw definitive conclusions from such results. In particular, when the material is optically active, it would seem essential that the individual optical isomers be examined. Racemic α-ET, for example, failed to produce >80% drug-appropriate responding in rats trained to discriminate (+)amphetamine from vehicle (Glennon, 1993). In that study, racemic α-ET (at 6.0 mg/kg) produced 41% (+)amphetamine-appropriate responding; at this dose the animals' response rates were reduced to about 60% of control. At doses of 7.5–14 mg/kg, the animals' response rates were dramatically depressed (to about 30% of control), and at 16 mg/kg the animals failed to respond. The present study shows that 12 mg/kg of (−)α-ET elicited >80% (+)amphetamine-appropriate responding. If (+)α-ET was an inactive substance, the estimated dose of α-ET necessary to result in stimulus generalization would have been about twice the dose of (−)α-ET or 24 mg/kg. Such a dose of racemic α-ET could not be effectively administered because lower doses of the agent had already substantially decreased the animals' response rates or completely disrupted the animals' behavior. But, (+)α-ET is not inactive. A dose of 3.5 mg/kg of (+)α-ET was shown to produce >80% DOM-appropriate responding. Thus, the behavioral disruption noted upon administration of racemic α-ET to (+)amphetamine-trained animals could reflect the disruptive nature of the DOM-like action of (+)α-ET in the racemic mixture, and this study might be one instance in which partial generalization (i.e., of racemic α-ET in (+)amphetamine-trained animals) can be explained on the basis of other drug discrimination results.

It would seem prudent, however, to avoid viewing (−)α-ET and (+)α-ET as simply amphetamine- or DOM-like agents, respectively. The fact that some animals were completely disrupted (i.e., no responses) and other animals exhibited marked reductions in their response rates at the dose of the optical isomer that resulted in complete stimulus generalization, in the (+)amphetamine- and DOM-trained animals, might be an indication that yet another pharmacological action is associated with each enantiomer. Indeed, both optical isomers of α-ET were shown in the present investigation to possess MDMA- and PMMA-like actions and relatively less behavioral disruption accompanied these substitutions (Table 1).

At this point, our preliminary conclusions are that the (+)amphetamine-like nature of racemic α-ET appears to reside primarily with (−)α-ET, whereas (+)α-ET seems primarily responsible for DOM-like stimulus affects. This conclusion, obviously, is based on the training doses and conditions employed in the present investigation. Nevertheless, layered on these actions, both optical isomers of α-ET are capable of producing MDMA- and PMMA-like actions.

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