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α-Ethyltryptamine (α-ET) as a discriminative stimulus in rats ☆

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Abstract

α-Ethyltryptamine (etryptamine, α-ET) is a drug of abuse that first appeared on the clandestine market in the mid-1980s. Its pharmacological actions are poorly understood. In this investigation, it is reported for the first time that α-ET serves as a training drug in drug discrimination studies. Male Sprague–Dawley rats were trained to discriminate (30-min pretreatment time) 2.5 mg/kg of α-ET (ED_{50}=1.3 mg/kg) from saline vehicle using a standard two-lever operant paradigm and a VI-15s schedule of reinforcement for appetitive reward. Once established, the α-ET stimulus was shown to have an onset to action of 30 min and a duration of effect of at least 4 h. In tests of stimulus generalization (substitution), the α-ET stimulus generalized to *S*(−)α-ET (ED_{50}=1.6 mg/kg) and *R*(+)α-ET (ED_{50}=1.3 mg/kg). Tests of stimulus generalization were also conducted with prototypical phenylisopropylamines: (+)amphetamine, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), and *N*-methyl-1-(4-methoxyphenyl)-2-aminopropane (PMMA). The α-ET stimulus generalized to DOM (ED_{50}=0.4 mg/kg) and PMMA (ED_{50}=0.7 mg/kg), but only partially generalized (*ca*. 40% maximal drug-appropriate responding) to (+)amphetamine. The results suggest that α-ET produces a complex stimulus.

Keywords: α-Ethyltryptamine; α-ET; (+)α-ET; (−)α-ET; DOM; PMMA; Amphetamine; Drug discrimination

1. Introduction

α-Ethyltryptamine, also known as etryptamine, α-ET, or AET, was first synthesized in 1947 as a potential synthetic precursor to the β-carbolines, and other syntheses have since been reported (e.g. Heinzelman et al., 1960; Hester et al., 1964; Snyder and Katz, 1947). Within about a decade of its first synthesis, α-ET was shown to interact with serotonin receptors of various isolated tissue preparations (Barlow and Khan, 1959a,b; Gaddum et al., 1955; Vane, 1959) and to act as an inhibitor of monoamine oxidase (MAO) (Govier et al., 1953; Greig et al., 1959). The latter action, due to the growing interest at that time in the relationship between inhibition of MAO and depression, led to clinical trials of α-ET as an antidepressant. α-ET was soon thereafter (1961) introduced as an antidepressant ("Monase"); but, despite its apparent effectiveness (e.g. Robie, 1961), it was withdrawn from the market within a year of its introduction due to problems with agranulocytosis and other side effects. This led to the subsequent synthesis (Hester et al., 1964) and patenting (Anthony, 1970) of the individual optical isomers of α-ET — presumably in an attempt to divorce its therapeutic action from its side effects. However, α-ET (nor either of its optical isomers) ever returned to the clinical scene. Interestingly, even though both α-ET isomers possess some action as inhibitors of MAO (Hester et al., 1964), the patent curiously states that although the mechanism of action of α-ET is unknown, "MAO inhibition is not the mechanism of action by which [its] remarkable antidepressant action is achieved in humans" (Anthony, 1970).

Very little was published in the scientific literature on α-ET during the 1970s. In the 1980s, however, α-ET made an appearance on the clandestine market as a "novel" designer drug (e.g. *Love Pearls*, *ET*). Perhaps the first report describing its illicit use was that in Germany by Daldrup et al., (1986). It appeared at about the same time in the U.S., was emergency scheduled in 1993, and placed into permanent Schedule I status in 1994 because of its structural similarity to known hallucinogenic tryptamine derivatives (Federal Register, 1994).

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It was also during the 1980s that structure–activity relationships were being formulated for various tryptamine derivatives to produce discriminative stimulus effects in animals similar to those of the classical hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM). For example, it was shown that both α-ET and α-methyltryptamine, a chain-shortened homolog of α-ET, substitute in DOM-trained rats (Glennon et al., 1982, 1983). The DOM-like effect of α-ET was found to be about half as potent as α-methyltryptamine and about 15 times less potent than DOM. The results suggested that α-ET might possess some underlying hallucinogenic character. Indeed, Murphree et al. (1961) had earlier shown that α-ET is hallucinogenic in humans. Although its actions were not necessarily identical to those of the hallucinogen lysergic acid diethylamide (LSD), α-ET was nonetheless shown to produce hallucinogenic effects. It might be noted that none of the published clinical studies with α-ET as an antidepressant ever reported a frank hallucinogenic response as a major action or side effect. One possible explanation for this is that clinical antidepressant doses typically ranged from about 5 mg to 25 mg administered three times a day (total daily oral dose typically <100 mg) (e.g. De Jong, 1961; Robie, 1961), whereas that used by Murphree et al. (1961) was a single 150 mg oral dose. More recent studies have confirmed, albeit with a limited subject population, that single doses of >100 mg might be required to obtain this psychoactive effect (Shulgin and Shulgin, 1997).

The introduction of α-ET to the clandestine market, amid indications that it was being sold as an MDMA-like [i.e., *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane; *XTC*, *Ecstasy*, *Adam*] substance (Federal Register, 1994), prompted further examination of the behavioral effects of α-ET. In animals trained to discriminate either (+)amphetamine or MDMA from saline vehicle, amphetamine-stimulus generalization failed to occur, but MDMA-stimulus substitution did occur, to α-ET (Glennon, 1993; Schechter, 1998). As such, α-ET was the first tryptamine derivative, indeed, the first non-phenylisopropylamine, shown to produce stimulus effects similar to those of MDMA. Additionally, Geyer and co-workers found that α-ET produces effects on rodent exploratory behaviors and startle reflex similar to that produced by MDMA (Krebs and Geyer, 1993; Martinez and Geyer, 1997). More recent studies have examined the stimulus effects of the two individual optical isomers of α-ET. In particular, *S*(−))α-ET substituted in (+)amphetamine-, PMMA-, and MDMA-trained rats, but not in DOM-trained rats, whereas *R*(+)α-ET substituted in DOM-, PMMA- [i.e., *N*-methyl-1-(4-methoxyphenyl)-2-aminopropane-] and MDMA-trained rats, but not in (+)amphetamine-trained rats (Hong et al., 2001). The results indicated that the effects of α-ET are stereospecific in DOM- and (+)amphetamine-trained animals, but not in PMMA- or MDMA-trained animals. Furthermore, the two optical isomers of α-ET were nearly equipotent with one another in the PMMA- and MDMA-trained animals.

Drugs of abuse that possess a relatively simple phenylalkylamine structure can produce one (or more) of three distinct stimulus effects in animals: a DOM-like effect, a (+)amphetamine like effect, or a PMMA-like effect (reviewed: Glennon, 2002). That is, animals trained to discriminate one of these three agents fail to recognize the other two. This scheme has been used to classify various other agents with known (or with potential) abuse liability. For example, MDMA, an empathogenic agent that possesses some degree of amphetamine-like central stimulant character (see Bondareva et al., 2005 for discussion), substitutes both in (+)amphetamine-trained and PMMA-trained (but not DOM-trained) animals supporting claims for both types of action.

To date, α-ET has not been employed as a training drug in drug discrimination studies. In the present study, the pharmacological characterization of α-ET is extended by using it as a training agent in a drug discrimination paradigm. Specifically, rats were trained to discriminate the stimulus effects of α-ET from saline vehicle in a two-lever operant task. Once accomplished, the dose–response and time-course of the stimulus were determined. In addition, stimulus generalization (substitution, recognition) studies were performed with the optical isomers of α-ET and the prototypical phenylalkylamines DOM, (+)amphetamine, and PMMA.

2. Materials and methods

Seven male Sprague–Dawley rats (Charles River Laboratories), weighing 250–300 g at the beginning of the study, were trained to discriminate (15-min presession injection interval) α-ET from saline vehicle (sterile 0.9% saline) under a variable interval 15-s schedule of reinforcement for sweetened condensed milk reward using standard two-lever Coulbourn Instruments operant equipment. Animal studies were conducted under an approved Institutional Animal Care and Use Committee protocol.

In brief, animals were food-restricted to maintain body weights of approximately 80% that of their free-feeding weight, but were allowed access to water *ad lib* in their individual home cages. Daily training sessions were conducted with the training dose of α-ET or saline. For approximately half the animals, the right lever was designated as the drug-appropriate lever, whereas the situation was reversed for the remainder of the animals. Learning was assessed every fifth day during an initial 2.5-min non-reinforced (extinction) session followed by a 12.5-min training session. 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 training drug and ≤20% of their responses on the same drug-appropriate lever after administration of saline. During the testing (i.e., stimulus generalization) 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 test day). On one of the two days before an antagonism or generalization test, approximately half the animals would receive the training dose of α-ET 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 training criteria during the extinction session were excluded from the 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 non-reinforcement conditions. An odd number of training sessions (usually 5) separated any two test sessions. Doses of test drugs were administered to the groups of rats in a random order using a 15-min presession injection interval. 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 5 total responses during the 2.5-min extinction session were considered as being behaviorally disrupted. Percent drug-appropriate responding and response rate data refer only to animals making ≥5 responses during the extinction session (Young and Glennon, 1986). If >50% of the animals were disrupted following administration of a given drug dose, data were not plotted. Where applicable, an ED_{50} dose was calculated by the method of Finney (1952). These doses represent the drug dose where animals would be expected to make 50% of their responses on the drug-appropriate lever.

2.1. Drugs

α-Ethyltryptamine acetate, and its individual optical isomers as their acetate salts, were prepared by the method of Anthony (1970) as we have previously reported (Hong et al., 2001). *N*-Methyl-1-(4-methoxyphenyl)-2-aminopropane (i.e., PMMA) was prepared in our laboratory as its hydrochloride salt. 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane hydrochloride (DOM) was obtained as a gift from NIDA, and (+)amphetamine sulfate was available from previous studies conducted in our laboratories. Doses refer to the weight of the salts. Solutions in sterile 0.9% saline were freshly prepared each day and administered by intraperitoneal injection. Doses refer to the salts of the several agents investigated.

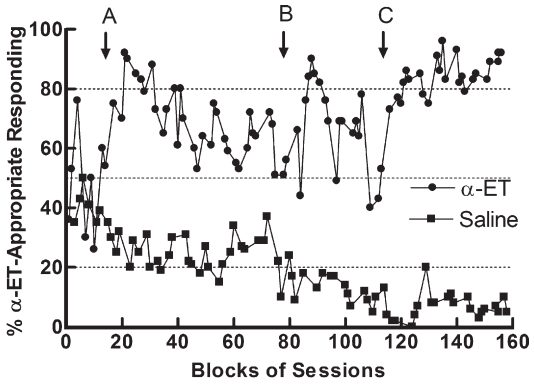

Fig. 1. Learning curve showing the training of rats to discriminate α-ET from saline vehicle. The study began with an α-ET training dose of 2.5 mg/kg and a presession injection interval of 15 min. Over time, the training dose and presession injection interval were varied (see text for details). The training dose was increased to 3.5 mg/kg (A) and then 5 mg/kg (B). Subsequently, the training dose was decreased to 2.5 mg/kg, but the presession injection interval was increased from 15 to 30 min (C). Closed circles represent the effect (group mean) of α-ET, and open circle represent saline treatment. S.E.M. not shown for purpose of clarity.

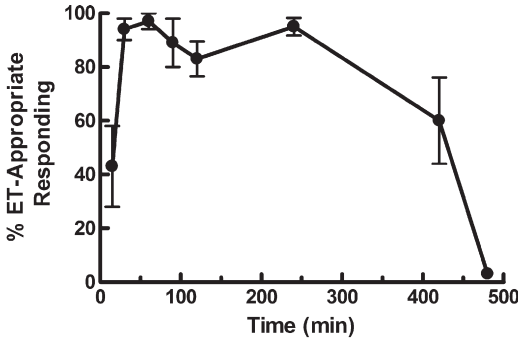

Fig. 2. Time-course of the α-ET stimulus. α-ET (2.5 mg/kg) was administered to the α-ET-trained animals and their responding (group mean±S.E.M.) was monitored at varying times post administration during a 2.5-min extinction session. Each point reflects a different experiment performed on a different day.

3. Results

Initially, attempts were made to train a group of animals to discriminate 2.5 mg/kg of α-ET using a 15-min presession injection interval (Fig. 1). After approximately two months of training under these conditions, the animals failed to consistently make ≥80% of their responses on the drug-designated lever following administration of α-ET, and ≤ 20% of their responses on this same lever following administration of saline vehicle. The training dose of α-ET was increased to 3.5 mg/kg (A; Fig. 1). After five months of training, the animals still failed to meet the training criteria. The animals were put on "free-feed" and were not administered drug for approximately one month. Subsequently, training was resumed and the α-ET training dose was increased to 5 mg/kg (B; Fig. 1). Although the animals seemingly learned to discriminate this training dose of α-ET, percent drug-lever responding was not stable. At the end of approximately four months of training under these conditions, the animals still failed to meet the training criteria. Nearly one year after the study was begun, the α-ET training dose was reduced to 2.5 mg/kg, but the presession injection interval was increased from 15 min to 30 min (C; Fig. 1). With the longer presession injection interval, the animals quickly learned to discriminate α-ET from saline vehicle. Hence, after >14 months of training, conditions (i.e., 2.5 mg/kg; 30-min presession injection interval) were eventually identified that resulted in a stable α-ET/saline-vehicle discrimination (Fig. 1).

Once the animals had reliably learned the α-ET/saline discrimination task, a time-course study was conducted. The time interval between injection of 2.5 mg/kg of α-ET and testing was varied from 15 min to 480 min (Fig. 2). Following a 15-min presession injection interval, the animals made approximately 40% of their responses on the drug-appropriate lever, whereas percent α-ET-appropriate responding increased to 94% following a 30-min interval. The stimulus effect of α-ET appeared to be rather long-acting and the animals still responded on the drug-appropriate lever when 2.5 mg/kg of α-ET was administered 240 min prior to testing (Fig. 2). After a presession injection

interval of 480 min, the animals responded in a saline-like fashion following administration of α-ET.

Tests of stimulus generalization were conducted with lower α-ET doses (Fig. 3), with the optical isomers of α-ET (Fig. 4), as well as with DOM, (+)amphetamine, and PMMA (Fig. 3). Administration of α-ET doses lower than the training dose elicited reduced percent drug-appropriate responding (ED_{50}= 1.3 mg/kg; 95% CL=0.9–1.9 mg/kg). The animals' response rates were fairly consistent across the dose range examined.

The α-ET stimulus generalized to both α-ET optical isomers (Fig. 4) and the isomers were nearly equipotent [*S*(-)-α-ET ED_{50}=1.6 mg/kg; 95% CL=0.9–2.8 mg/kg; *R*(+)α-ET ED_{50}= 1.3 mg/kg; 95% CL=0.9–2.0 mg/kg)]. The *S*(-)-isomer was somewhat more behaviorally disruptive than its *R*(+)-enantiomer and at the *S*(-)α-ET dose that produced >80% drug-appropriate responding, two of the animals did not respond and the response rate of the responding animals was only about 20% of that seen after administration of the lowest dose tested or of saline vehicle.

Both DOM (ED_{50}=0.4 mg/kg; 95% CL=0.2–0.8 mg/kg) and PMMA (ED_{50}=0.7 mg/kg; 95% CL=0.4–1.3 mg/kg) substituted for the α-ET stimulus and were more potent than α-ET (Fig. 3). At the three highest DOM doses evaluated, only 5 of 7 animals responded and response rates were depressed relative to vehicle control. PMMA was evaluated in five animals; the animals' response rates decreased as dose was increased, and at the highest two doses evaluated only 4 of 5 animals responded. Administration of (+)amphetamine doses (0.3 to 0.6 mg/kg) failed to engender >40% drug-appropriate responding; administration of 0.8 mg/kg of (+)amphetamine produced behavioral disruption. The animals' response rates were depressed at all (+) amphetamine doses evaluated, and none of the animals responded following administration of the 0.8 mg/kg dose.

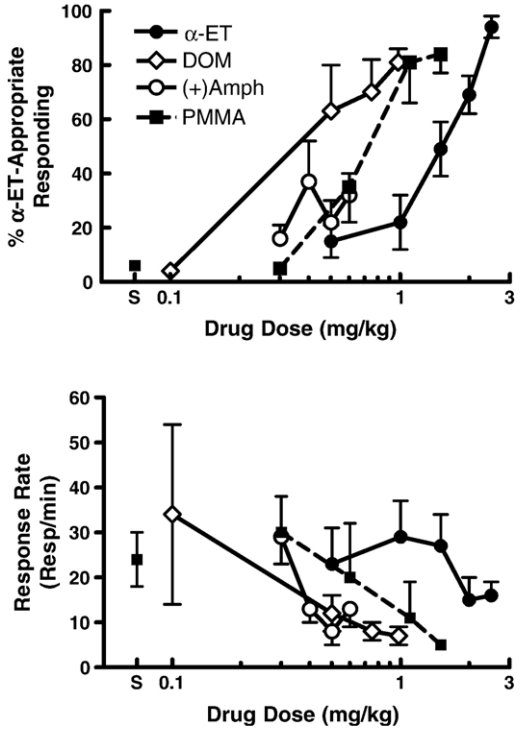

Fig. 3. Results of stimulus generalization studies in rats trained to discriminate 2.5 mg/kg of α-ET from saline vehicle (upper panel). Shown is the mean (±S.E.M.) percent drug-appropriate responding following administration of α-ET, DOM, PMMA, and (+)amphetamine. Administration of 0.8 mg/kg of (+) amphetamine resulted in behavioral disruption (data not shown). S = the effect of 1 ml/kg of 0.9% saline. The animals' response rates (±S.E.M.) are shown in the lower panel.

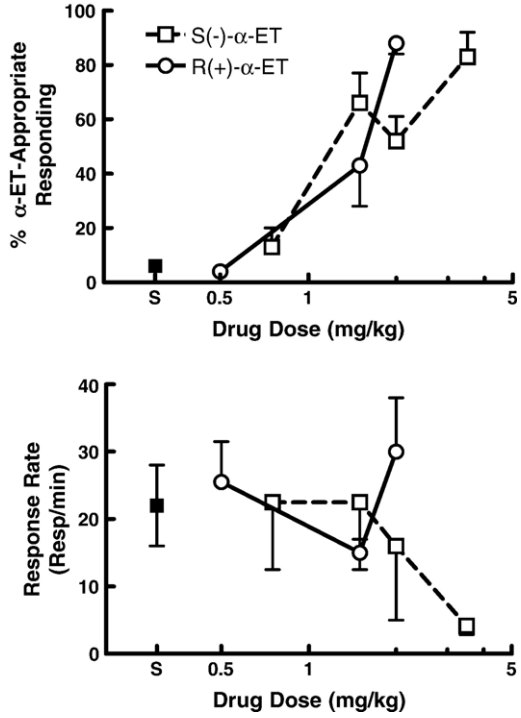

Fig. 4. Results of stimulus generalization studies with *S*(-)- and *R*(+)α-ET in rats trained to discriminate 2.5 mg/kg of α-ET from saline vehicle (upper panel). Shown is the mean (±S.E.M.) percent drug-appropriate responding. S = the effect of 1 ml/kg of 0.9% saline. The animals' response rates (±S.E.M.) are shown in the lower panel.

4. Discussion

The results of this study show that α-ET can serve as a discriminative stimulus in animals. Although it was necessary to evaluate different potential training doses and presession injection intervals, it was eventually established that 2.5 mg/kg of α-ET with a presession injection interval of 30 min, serves as an effective and reliable discriminative stimulus (Fig. 1). Once the animals were trained, the α-ET stimulus was shown to be dose-dependent (Fig. 3), with the ED_{50} dose (ED_{50}=1.3 mg/kg) being approximately one-half the training dose. Finally, a time-course study (Fig. 2) showed that α-ET is a relatively long-acting agent, with the animals still making >80% of their responses on the drug-appropriate lever 4 hours post administration. Although there are only limited data on the duration of action of α-ET in humans, Shulgin and Shulgin (1997) have indicated that its effects are dissipated at 3 to 6 h following oral administration.

To further characterize the α-ET stimulus, tests of stimulus generalization were conducted with the individual optical

isomers of α-ET, as well as with the three prototypic phenylalkylamines of abuse: the hallucinogen DOM, the stimulant (+)amphetamine, and the empathogen PMMA (Glennon, 2002). Both *S*(-)- and *R*(+)α-ET substituted for the α-ET stimulus (Fig. 4) and were essentially equipotent (ED_{50}=1.6 and 1.3 mg/kg, respectively). That is, the stimulus effects of α-ET were not stereoselective with respect to its individual optical isomers. Although there is stimulus similarity between the two isomers and the training drug, the effects of the isomers might not be identical because the animals' response rates were depressed at the *S*(-)α-ET dose that elicited >80% drug-appropriate responding whereas this was not the case with *R*(+)α-ET. Support for the concept of stimulus dissimilarity can be found in an earlier study where a (+)amphetamine stimulus generalized to *S*(-)α-ET but not *R*(+)α-ET (Hong et al., 2001).

The α-ET stimulus generalized to DOM (ED_{50}=0.4 mg/kg) and PMMA (ED_{50}=0.7 mg/kg). But, here too, the animals' response rates were depressed at doses that produced >80% drug-appropriate responding (Fig. 3). It would seem that similarities exist between the stimulus effects produced by α-ET, DOM and PMMA, but that there must also be some differences. Consistent with this conclusion is that a DOM stimulus did not generalize to PMMA, that a PMMA stimulus did not generalize to DOM, but that both a DOM stimulus and a PMMA stimulus generalized to α-ET (Glennon et al., 1982; Hong et al., 2001).

How, then, might the stimulus effects of α-ET be characterized? This remains to be determined and awaits the results of additional study. Nevertheless, some preliminary conclusions can be proffered. Under the present training and testing conditions, α-ET does not seem to be a simple DOM-like, PMMA-like, or (+)amphetamine-like substance. α-ET and DOM substitute for one another in tests of stimulus generalization regardless of which is used as training drug (Glennon et al., 1982; present study) suggesting α-ET possesses hallucinogenic character. As mentioned in the introduction, Murphree et al. (1961) have reported that α-ET is, indeed, hallucinogenic in humans. Although DOM and PMMA fail to substitute for one another regardless of which is used as training drug, the α-ET stimulus generalized to PMMA (Fig. 3). Clearly, then, α-ET cannot be considered simply a DOM-like agent. α-ET and (+)amphetamine failed to completely substitute for one another in tests of stimulus generalization when the other is used as training drug, but earlier studies showed that *S*(-)α-ET (but not *R*(+)α-ET) substitutes for (+)amphetamine. On the basis of the above findings, it would seem that the stimulus properties of the individual α-ET isomers are similar, yet different, and that the actions of racemic α-ET might likely reflect these similarities and differences. For example, there is evidence that α-ET is a locomotor stimulant in rodents (Greig et al., 1961; Lessin et al., 1965). More recently, the College on Problems of Drug Dependence examined α-ET in several behavioral assays and concluded that α-ET is more of a central stimulant than depressant (Winger et al., 1994). They found that its stimulant action in mice, although evident, was not "profound" and that its potency was less than that of amphetamine. Also found was that it produced only partial amphetamine-like stimulus effects in (one of three) monkeys following intragastric administration. Other studies, employing (+)amphetamine-trained rats, showed that only *S*(-)α-ET (but neither racemic nor *R*(+)α-ET) substituted for the training drug, but that it was about 20-fold less potent than (+)amphetamine (Hong et al., 2001). Taken together, there is evidence that α-ET might produce a weak amphetamine-like stimulus action, but that this effect could be overshadowed by other actions produced by α-ET (e.g. DOM-like, PMMA-like) which are manifested at lower drug doses. It might be noted that the dose of *S*(-)α-ET that substituted for the (+)amphetamine stimulus (7.8 mg/kg; Hong et al., 2001) was about ten times higher than the dose of (+)amphetamine that disrupted the animals responding in the present investigation. It would seem, then, that the stimulus character of α-ET is complex.

α-Ethyltryptamine is a fascinating centrally-acting agent. Although α-ET has been evaluated in hundreds of human subjects, its pharmacology is still poorly understood. α-ET has been reported to be an inhibitor of MAO (see Introduction). Thus, the possibility exists that MAO inhibition might underlie (some of) the stimulus actions of α-ET; future studies will address this. However, α-ET is also a reasonably potent releaser of 5-HT, and it also behaves as an inhibitor of 5-HT reuptake (Ask et al., 1989; Baker et al., 1980; Huang et al., 1991; Renyi and Ross, 1985; Renyi et al., 1986). That is, α-ET is capable of increasing synaptic concentrations of serotonin by multiple mechanisms. In addition, α-ET has been shown to have qualitatively similar effects on synaptic dopamine levels (Renyi and Ross, 1985). Consequently, mechanistic roles involving indirect activation of serotonin (and perhaps dopamine) receptors cannot be excluded, and might even explain the complex nature of the α-ET stimulus. Further characterization of the α-ET stimulus is currently underway in our laboratories.

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