Pharmacology Biochemistry and Behavior, Vol. 46, pp. 459–462, 1993

0091-3057/93 $6.00 + .00

RAPID COMMUNICATION

MDMA-Like Stimulus Effects of α-Ethyltryptamine and the α-Ethyl Homolog of DOM

RICHARD A. GLENNON

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

Received 11 December 1992

GLENNON, R. A. *MDMA-like stimulus effects of α-ethyltryptamine and the α-ethyl homolog of DOM.* PHARMACOL BIOCHEM BEHAV **46**(2) 459–462, 1993.—One-carbon homologation of phenylalkylamine or indolylalkylamine hallucinogens containing an α-methyl substituent typically results in a reduction of hallucinogenic potency; however, this same structural change has little to no effect on agents that produce MDMA-like effects. In the present investigation, rats trained to discriminate 1.5 mg/kg of MDMA (3,4-methylenedioxymethamphetamine) from saline vehicle were employed to determine if the α-ethyl homologs of the hallucinogens 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) and α-methyltryptamine (α-MeT)—that is, α-EH DOM (BL-3912) and α-EtT, respectively—would produce stimulus effects similar to those of MDMA. Although the MDMA stimulus failed to generalize to DOM (previously published) and α-MeT (this study), MDMA stimulus generalization occurred both to α-EH DOM (ED_{50} = 1.3 mg/kg) and α-EtT (ED_{50} = 3.5 mg/kg). A (+)amphetamine stimulus (training dose = 1.0 mg/kg) only partially generalized to these two agents, suggesting that the MDMA stimulus generalization involves more than a simple amphetamine-like action. As such, this is the first demonstration that classical hallucinogens can produce MDMA-like effects upon homologation and that MDMA-like stimulus effects can be associated with an indolylalkylamine. Furthermore, these results continue to support the concept that an intact methylenedioxy ring system, such as that found in MDMA and other MDMA-related agents, is not a structural requirement for drugs to produce MDMA-like effects.

α-Ethyltryptamine α-ET α-Methyltryptamine α-MeT MDMA DOM Amphetamine

IN our continuing efforts to understand the structure-activity relationships and mechanism(s) of action of controlled substance analogs (designer drugs), we have focussed on phenylisopropylamine (PIA) derivatives that are structurally related to the PIA stimulant amphetamine and the PIA hallucinogen DOM (1-[2,5-dimethoxy-4-methylphenyl]-2-aminopropane). One such agent receiving particular notoriety over the past decade is the PIA derivative MDMA (3,4-methylenedioxymethamphetamine; "Ecstasy") (reviewed: 3,12). Early investigations of structure-activity relationships were limited, for the most part, to other methylenedioxy-containing derivatives; however, recent findings reveal that the intact methylenedioxy ring system of MDMA is not required for retention of MDMA-like activity. For example, we have demonstrated in drug discrimination studies that PMMA (*para*-methoxymethamphetamine; functionally, a ring-opened analog of MDMA in which the 3-position oxygen atom has been excised) substitutes for MDMA in MDMA-trained animals and is, in fact, several times more potent than MDMA (4,5). More recently, Johnson et al. (9) have shown that another ring-opened relative of MDMA (i.e., 1-[3-methoxy-4-methylphenyl]-2-aminopropane) also produces MDMA stimulus effects in rats. Because it is now realized that a methylenedioxy group is not essential for MDMA-like stimulus properties, there is no reason to restrict new investigations to methylenedioxy-containing compounds. Indeed, it is entirely possible that other types of compounds may be capable of producing effects similar to those produced by MDMA.

The hallucinogen DOM, which does not substitute for MDMA in drug discrimination studies (3), possesses an α-methyl substituent. It is commonly held that extension of the α-methyl substituent of hallucinogenic agents (e.g., by homo-

Presented in part at the NIDA Technical Review on Hallucinogenic Agents, Bethesda, MD, July 1992.

logation to an α-ethyl group) reduces or abolishes hallucinogenic character (2,12). However, the α-methyl group of MDMA can be extended to an α-ethyl group with retention of MDMA properties (13). α-Methyltryptamine (α-MeT) is an example of an indolylalkylamine hallucinogen; homologation to α-ethyltryptamine (α-EtT) results in a psychoactive agent with, as might be expected, reduced potency relative to α-MeT. (For a comparison of the effects of α-MeT and α-EtT in humans, see Murphree et al. [11].) Due to the structural relationships amongst these agents, it was of interest to determine if the ethyl homologs of DOM (i.e., α-EH DOM) or of α-MeT (i.e., α-EtT) possess any MDMA-like character. That is, the possibility exists that the α-ethyl substituent of α-EH DOM and/or α-EtT might result in reduced DOM-like or hallucinogenic character while at the same time imparting (or unmasking) MDMA-like qualities.

Just as our studies with α-EH DOM began, we learned that α-EtT had been confiscated by law enforcement officials as a new "designer drug" called "ET." According to anecdotal reports gathered by the Drug Enforcement Administration, this agent produces in human subjects an effect reminiscent of that produced by MDMA (F. Sapienza, personal communication). α-EtT is not a novel agent. α-EtT (or etryptamine) was patented in the early 1960s; it possesses activity as a central stimulant and euphoriant, and is a monoamine oxidase inhibitor (reviewed: 8). It was used clinically for a while as an antidepressant (Monase™) but was withdrawn from the market shortly after its introduction.

We have previously reported that a DOM stimulus generalizes both to α-MeT (ED_{50} = 3.1 mg/kg) and α-EtT (ED_{50} = 6.6 mg/kg) (6). Homologation of the α-methyl group of DOM to an α-ethyl group (i.e., α-EH DOM) results in a psychoactive agent (15,16; reviewed: 2) with retention of DOM stimulus properties but in a >10-fold reduced potency relative to DOM in drug discrimination studies (DOM ED_{50} = 0.45 mg/kg, α-EH DOM ED_{50} = 6.4 mg/kg) (6). Thus, consistent with earlier literature on hallucinogenic activity, it would appear that homologation of the α-methyl group of hallucinogenic agents to an α-ethyl group reduces DOM-like stimulus potency. However, it remains to be determined if the α-ethyl homologs can produce any MDMA-like stimulus effects. Consequently, we conducted a preliminary investigation of the stimulus effects of these agents in rats trained to discriminate MDMA from vehicle. Because MDMA possesses some amphetamine-like character—that is, an MDMA stimulus has been shown to partially generalize to (+)amphetamine (3)—these same agents were also evaluated in rats trained to discriminate (+)amphetamine from vehicle to examine the possibility that they might simply act as amphetamine-like stimulants.

METHODS

The subjects were 12 male Sprague–Dawley rats weighing 250–300 g at the start of the study. The animals were first trained to lever-press for sweetened milk reward using standard two-lever operant chambers (Coulbourn Instruments, Lehigh Valley, PA, model E10-10) housed within sound- and light-attenuating outer chambers. Once lever-pressing behavior was acquired, the animals were trained to discriminate intraperitoneal injections of (+)amphetamine (1.0 mg/kg; n = 5) or MDMA (1.5 mg/kg; n = 7) from 0.9% sterile saline (1.0 ml/kg). That is, rats were trained to respond on a variable-interval 15-s (VI 15-s) schedule of reinforcement; once rates of responding stabilized, the animals received an injection of drug or saline 15 min prior to each session. Drug or saline was administered on a double alternation schedule (i.e., two days drug, two days saline) and training sessions were of 15 min duration. For half of the animals, the right lever was designated the drug-appropriate lever; the situation was reversed for the remaining animals. On every fifth day, learning was assessed during an initial 2.5-min nonreinforced (extinction) period followed by a 12.5-min training session. We have previously described this training procedure for (+)amphetamine- and MDMA-trained animals in greater detail (5,7). Data collected during the extinction period included percent drug-appropriate lever responding (i.e., the number of responses on the drug-designated lever ÷ total number of responses, expressed as a percent) and total responses made during the 2.5-min session (expressed as responses/min).

Once the rats consistently (i.e., for three consecutive weeks) made >80% of their responses on the drug-appropriate lever after administration of drug, and <20% of their responses on the same lever after injection of saline, stimulus generalization studies were begun. During these investigations, test sessions were interposed among the training sessions; however, after the 2.5-min extinction period, the animals were returned to their individual home cages. During generalization tests the rats were injected with doses of a test compound and, 15 min later, were tested under extinction conditions. Stimulus generalization was said to have occurred when the animals made ≥80% of their responses on the drug-appropriate lever during an extinction session. Where stimulus generalization occurred, an ED_{50} value (i.e., the dose at which the animals would be expected to make 50% of their responses on the drug-appropriate lever) was calculated by the method of Finney (1).

Drugs

α-Ethyltryptamine acetate and (+)amphetamine sulfate were purchased from Aldrich Chemical Company (Milwaukee) and Sigma (St. Louis), respectively. Racemic *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane hydrochloride (MDMA) and α-methyltryptamine hydrochloride were previously synthesized in our laboratories. Racemic 1-(2,5-dimethoxy-4-methylphenyl)-2-aminobutane hydrochloride (BL-3912; lot #11609-21) was a gift from Bristol Laboratories (Syracuse, NY). All solutions were prepared fresh daily and all agents were administered 15 min prior to testing via i.p. injection in a 1.0 ml/kg injection volume.

RESULTS AND DISCUSSION

We have previously demonstrated that a (+)amphetamine stimulus does not generalize to DOM (3). The present investigation reveals that the (+)amphetamine stimulus also does not generalize to α-MeT, α-EtT, or α-EH DOM (Table 1); however, all three of these latter agents evoke some amphetamine-appropriate responding (i.e., result in partial generalization) but ultimately result in depressed response rates and disruption of behavior as dose is increased.

The MDMA stimulus does not generalize to DOM (3). The present study reveals that the MDMA stimulus does not generalize to α-MeT (Table 1). Nevertheless, at doses of between 0.1 and 3 mg/kg, α-MeT elicits up to 57% MDMA-appropriate responding; higher doses result in depressed response rates and disruption of behavior. The α-ethyl homologs of both α-MeT and DOM result in MDMA stimulus generalization.

DOM does not produce amphetamine-like (3) or MDMA-like (3) stimulus effects in rats; α-MeT produces DOM-like effects (6), but also results in partial generalization in rats

TABLE 1

RESULTS OF STIMULUS GENERALIZATION STUDIES

Agent	Dose (mg/kg)	N*	Drug-Appropriate Responding†‡	Response Rate‡ (Resp/min)
		Amphetamine-Trained Animals		
α-MeT	0.5	3/3	25% (10)	8.1 (1.6)
	3.0	3/3	42% (18)	7.0 (1.7)
	6.0	3/5	57% (9)	7.7 (1.7)
	7.0	3/4	17% (12)	11.7 (4.4)
	8.0	2/3	35% (15)	5.6 (3.6)
	9.0	0/3	—§	
α-EtT	0.5	4/4	14% (4)	14.2 (3.0)
	3.0	5/5	20% (7)	13.9 (5.7)
	6.0	5/5	41% (10)	8.1 (1.5)
	7.5	2/4	32% (10)	4.7 (1.0)
	9.0	3/4	25% (16)	4.1 (0.6)
	12.0	3/4	31% (16)	4.1 (0.6)
	14.0	2/4	16% (3)	4.8 (1.6)
	16.0	0/4	—§	
α-EH DOM	0.5	3/3	30% (1)	17.2 (4.4)
	2.5	3/3	39% (19)	16.4 (7.8)
	5.0	3/3	52% (15)	10.9 (6.7)
	6.5	3/3	43% (12)	11.3 (2.1)
	8.0	1/3	—§	
	10.0	3/3	19% (11)	8.2 (1.5)
	12.0	0/3	—§	
(+)Amphetamine	1.0	5/5	91% (3)	12.8 (1.8)
Saline (1 ml/kg)		5/5	17% (8)	12.4 (2.1)
		MDMA Trained Animals		
α-MeT	0.01	3/3	29% (8)	13.3 (1.2)
	0.1	5/6	55% (8)	14.0 (4.5)
	0.7	3/3	57% (9)	7.6 (3.5)
	3.0	3/3	55% (5)	13.6 (1.6)
	6.0	4/6	40% (12)	7.7 (1.9)
	8.0	0/3	—§	
α-EtT	0.8	3/3	22% (4)	14.0 (1.8)
	3.0	3/3	48% (3)	13.9 (5.7)
	6.0	3/4	63% (8)	13.3 (3.2)
	9.0	3/3	64% (3)	16.0 (0.8)
	12.0	3/3	65% (18)	20.0 (2.4)
	13.5	4/7	86% (4)	14.1 (4.3)
	14.0	1/3	—§	
			ED_{50} = 3.5 (1.0–11.6) mg/kg¶	
α-EH DOM	0.5	3/3	18% (6)	17.4 (3.1)
	1.0	3/4	46% (13)	14.9 (5.8)
	2.5	3/3	68% (6)	14.9 (6.1)
	5.0	3/3	91% (5)	22.6 (8.1)
			ED_{50} = 1.3 (0.5–3.6) mg/kg#	
MDMA	1.5	7/7	88% (4)	13.8 (1.0)
			ED_{50} = 0.76 mg/kg#	
Saline (1 ml/kg)		7/7	17% (3)	14.1 (2.1)

*Number rats of responding/number treated. †Percent of total responses on the drug-appropriate lever. ‡Data were collected during a 2.5-min extinction session and are followed in parenthesis by SE. §Disruption of behavior (i.e., majority of animals made < 5 responses during the entire 2.5-min extinction session). ¶ED_{50} value followed by 95% confidence limits. #ED_{50} value previously reported (5); included for comparison purposes.

trained to discriminate (+)amphetamine or MDMA from vehicle (maximum of 57% drug-appropriate responding in both instances; Table 1). Partial generalization in the amphetamine-trained animals is certainly consistent with previous reports that α-MeT produces locomotor effects in rodents resembling those produced by amphetamine (e.g., 10). Although it would be tempting to speculate that the partial generalization noted in the MDMA-trained animals upon administration of α-MeT might be related to an amphetamine-like effect, the data available at this time are less than sufficient to warrant such a conclusion. Like α-MeT, α-EtT and α-EH DOM (both of which substitute for DOM in DOM-trained rats [6]) also result in partial generalization in (+)amphetamine-trained animals (maximum of 41% and 52% amphetamine-appropriate responding, respectively; Table 1). However, both agents, unlike α-MeT, result in MDMA stimulus generalization. Thus, although α-EtT is known to produce central stimulant effects in animals (8), it is unlikely that the MDMA-like effects of these latter two agents are a simple reflection of amphetaminergic character.

To the best of our knowledge, this is the first demonstration that a minor molecular modification of a classical hallucinogen (i.e., DOM) converts it to an agent (i.e., α-EH DOM) that retains DOM stimulus effects but that additionally results in MDMA stimulus generalization. Furthermore, α-EtT is the first example of an indolylalkylamine analog demonstrated to substitute in MDMA-trained animals. Thus, it would appear that one-carbon homologation of the α-methyl groups of the PIA hallucinogen DOM and the indolylalkylamine hallucinogen α-MeT not only reduces their DOM-like stimulus potency (see introduction), but also results in agents that are capable of producing MDMA-like stimulus effects. This latter property is not shared by their parent compounds DOM and α-MeT, which at best result only in partial generalization in MDMA-trained animals. The finding that α-EtT produces MDMA-like effects is substantiated in light of very recent reports that it produces MDMA-like effects in human subjects.

α-EH DOM (14,15) and α-EtT (11) are psychoactive substances that seem to have defied psychopharmacological classification or categorization. Although there has been some mention of their "hallucinogenic potential," and even though α-EtT produces what may be considered LSD-like effects in some human subjects (11), the actions of these agents are clearly distinguishable from classical hallucinogens (see 2,11, 14 for further discussion). However, as with many classical hallucinogens, these agents substitute for DOM in DOM-trained animals (3). Interestingly, both agents also substitute for MDMA in MDMA-trained animals (this study). Furthermore, these agents produce their MDMA-like effects at doses lower than those that elicit DOM stimulus effects. That is, the ED_{50} values for MDMA stimulus generalization are lower than those for DOM stimulus generalization. Thus, at low doses, their MDMA effects may predominate over their DOM effects. In addition, both agents result in partial generalization in (+)amphetamine-trained rats (Table 1), and at least α-EtT has been demonstrated to be an amphetamine-like stimulant in several species of animals (8). Taken together, these preliminary studies suggest that α-EH DOM and α-EtT may represent agents with varying degrees of DOM-like (possibly hallucinogenic), amphetamine-like (possibly central stimulant), and MDMA-like qualities.

ACKNOWLEDGEMENTS

This work was supported in part by Public Health Service grant DA 01642. Rodney Higgs is acknowledged for his contribution to the drug discrimination studies.

REFERENCES

1. Finney, D. Probit analysis. London: Cambridge University Press; 1952.
2. Glennon, R. A. Hallucinogenic phenylisopropylamines: Stereochemical aspects. In: Smith, D. F., ed. Handbook of stereoisomers: Drugs in psychopharmacology. Boca Raton, FL: CRC Press; 1984:327-368.
3. Glennon, R. A. Stimulus properties of hallucinogenic phenalkylamines and related drugs: Formulation of structure-activity relationships. In: Asghar, K.; De Souza, E., eds. Pharmacology and toxicology of amphetamines and related designer drugs. Washington, DC: U.S. Government Printing Office; 1989:43-67.
4. Glennon, R. A. Phenylalkylamine stimulants, hallucinogens and designer drugs. Paper presented to the 52nd CPDD meeting. Richmond, VA; 1990 June.
5. Glennon, R. A.; Higgs, R. Investigation of MDMA-related agents in rats trained to discriminate MDMA from saline. Pharmacol. Biochem. Behav. 43:759-763; 1992.
6. Glennon, R. A.; Young, R.; Jacyno, J. M. Indolealkylamine and phenylalkylamine hallucinogens: Effect of N-methyl and α-methyl substituents on behavioral activity. Biochem. Pharmacol. 32:1267-1273; 1983.
7. Glennon, R. A.; Yousif, M.; Naiman, N.; Kalix, P. Methcathinone: A new and potent amphetamine-like agent. Pharmacol. Biochem. Behav. 26:547-551; 1987.
8. Hoffer, A.; Osmond, H. The hallucinogens. New York: Academic Press; 1967:466-468.
9. Johnson, M. P.; Frescas, S. P.; Oberlender, R.; Nichols, D. E. Synthesis and pharmacological examination of 1-(3-methoxy-4-methylphenyl)-2-aminopropane and 5-methoxy-6-methyl- 2-aminoindan: Similarities to 3,4-(methylenedioxy)methamphetamine (MDMA). J. Med. Chem. 34:1662-1668; 1991.
10. Lessin, A. W.; Long, R. F.; Parkes, M. W. Central stimulant actions of α-alkyl substituted tryptamines in mice. Br. J. Pharmacol. 24:49-67, 1965.
11. Murphree, H. B.; Dippy, R. H.; Jenney, E. H.; Pfeiffer, C. C. Effects in normal man of α-methyltryptamine and α-ethyltryptamine. Clin. Pharmacol. Ther. 2:722-726; 1961.
12. Nichols, D. E.; Glennon, R. A. Medicinal chemistry and structure-activity relationships of hallucinogens, In: Jacobs, B. L., ed. Hallucinogens: Neurochemical, behavioral and clinical perspectives. New York: Raven Press; 1984:95-142.
13. Nichols, D. E.; Oberlender, R. Structure-activity relationships of MDMA-like substances. In: Asghar, K.; De Souza, E., eds. Pharmacology and toxicology of amphetamines and related designer drugs. Washington, DC: U.S. Government Printing Office; 1989:1-19.
14. Shulgin, A. T.; Shulgin, A. Pihkal. Berkeley, CA: Transform Press; 1991.
15. Standridge, R. T.; Howell, H. G.; Tilson, H. A.; Chamberlain, J. H.; Molava, H. M.; Gylys, J. A.; Partyka, R. A.; Shulgin, A. T. Phenalkylamines with potential psychotherapeutic utility. II. Nuclear substituted 2-amino-1-phenylbutanes. J. Med. Chem. 23: 627-636; 1980.
16. Winter, J. C. Effects of the phenethylamine derivatives BL-3912, fenfluramine, and Sch 12,679 in rats trained with LSD as a discriminative stimulus. Psychopharmacology 68:159-162; 1980.