Stimulus Properties of Hallucinogenic Phenalkylamines and Related Designer Drugs: Formulation of Structure-Activity Relationships

Richard A. Glennon

INTRODUCTION

The purpose of the studies with phenalkylamine derivatives is severalfold: (1) to classify these agents by their primary effect; (2) to understand the structure-activity relationship (SAR) for each type of activity; and (3) to elucidate the mechanisms of action of these agents. Armed with information on SAR, one can, theoretically make predictions about the activity of agents yet to be synthesized; an understanding of the mechanisms of action can aid in the development of potential antagonists that could be useful for reversing the effects of these substances. Obviously, before one can investigate SAR and mechanisms of action, it is important to have some reliable method of classification. In the course of the studies, several different procedures have been used to examine the actions of these agents. Perhaps the most useful is the drug discrimination procedure. In this paradigm, animals are trained to recognize (or discriminate) the stimulus effects of a particular dose of a given agent; once trained, the animals can be administered doses of a test compound (i.e., a challenge drug) to determine if the challenge drug produces stimulus effects similar to those of the training drug. In such tests, referred to as tests of stimulus generalization, the animals essentially indicate whether or not a similarity exists between the actions of a new agent and those of a reference agent. Dose:response curves can be obtained and ED_{50} values determined. Thus, the procedure provides data that are both qualitative and quantitative. Needless to say, there are occasions when such studies produce results that are less than straightforward and are difficult to interpret. In other words, although drug discrimination studies provide very useful information on similarity of effect, potency, timecourse of action, mechanism of action, activity of metabolites, and other data, they cannot be used by themselves to characterize completely the pharmacological effects of a given agent. Reviews on the drug discrimination paradigm, particularly as it applies to the study of

phenalkylamines, appear in the following publications: Glennon et al. (1983), Glennon (1986), and Young and Glennon (1986).

In drug discrimination studies, groups of rats were trained to discriminate either the stimulant phenalkylamine (+)amphetamine (AMPH) or the hallucinogenic phenalkylamine 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from saline. Other structurally related training drugs that have been used include the iodo and bromo analogs of DOM, i.e., DOI and *R* (-)DOB, as well as methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA). Such investigations, coupled with the results of radioligand binding studies, have permitted the classification of a number of phenalkylamines (Glennon et al. 1983; Glennon 1986; Young and Glennon 1986) and have allowed proposal of a mechanism of action for the hallucinogenic phenalkylamines (Glennon et al. 1986a). The present review describes in detail some of the SARs that have been formulated on the basis of drug discrimination studies. This discussion of results is not meant to be comprehensive. Because species of animal, schedule of reinforcement, presession injection intervals, doses of training drugs, and other conditions have remained constant throughout the studies, it should be possible to make stricter comparisons than if data were compared across different laboratories. This SAR analysis is based, for the most part, on the results of discrimination studies already published.

Some of the agents used in the present study have not been previously reported in the literature. These agents were prepared in our laboratories, and details of their synthesis will be published elsewhere. However, three of these agents are potential metabolites of MDMA and are described here to the extent that such information might be helpful to other investigators studying the metabolism of MDMA. All three were isolated as their white, crystalline hydrochloride salts, and all were analyzed correctly for carbon, hydrogen, and nitrogen. Melting points and recrystallization solvents (in parentheses) are provided. N-methyl-1 -(4-hydroxy-3-methoxyphenyl)-2-aminopropane (N-Me 4-OH MMA): 210-212 °C (isopropanol/ ether); N-methyl-1-(3-hydroxy4-methoxyphenyl)-2-aminopropane (N-Me 3-OH PMA): 164-165 °C (isopropanol); N-methyl-1-(3,4-dihydroxyphenyl-2aminopropane (N,α-dimethyl dopamine or N-Me 3,4-diOH AMPH): 116-118 °C (isopropanol/ether).

Examination of the stimulus properties of a large number of phenalkylamines and related derivatives shows many can be characterized as producing either AMPH-like stimulus effects or DOM-like stimulus effects. The structures of some of these agents are shown in figure 1. Certain other agents could not be reliably classified as either AMPH-like or DOM-like because, at the highest dose tested, they either produced vehicle-appropriate (i.e., saline-appropriate) responding or resulted in disruption of behavior.

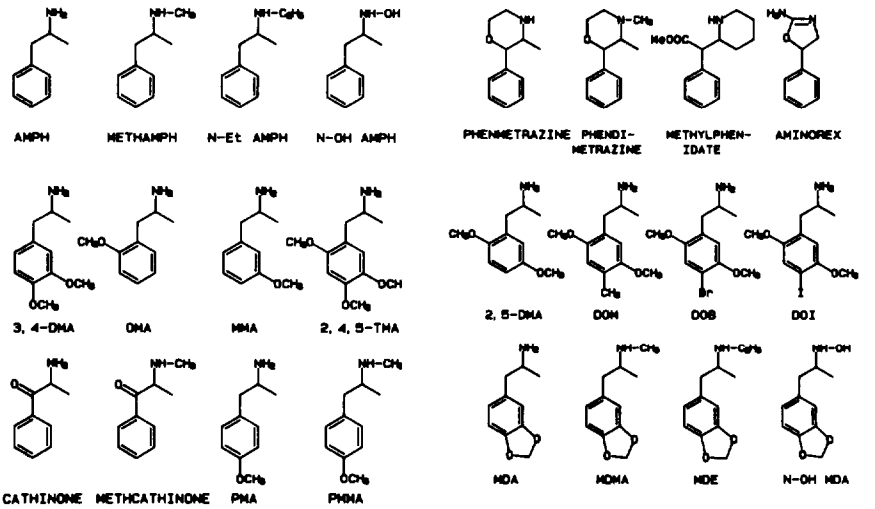


FIGURE 1. *Chemical structures of some of the agents employed in the present study*

Representative potency data (ED_{50} values) are presented in tabular form; data in these tables are given as µmol/kg so that direct potency comparisons can be made within a series. However, data presented in figures are given in mg/kg for the purpose of convenience.

Various phenallcylamines were shown to produce either DOM-like or AMPH-like stimulus effects; the structure-activity requirements for these activities are different from the standpoints of aromatic substitution patterns, terminal amine substituents. and optical activity. Thus, it has been possible to formulate two distinct SARs. It should be realized, however, that phenalkylamines need not produce only one of these two types of effects; certain phenallcylamines can produce pharmacological effects like neither DOM nor AMPH. Moreover, they can produce effects that are primarily peripheral, not central, in nature (Glennon 1987a). The fact that an agent produced DOM- or AMPH-like effects does not imply that it cannot produce an additional effect; conversely, if an agent does not produce either DOM- or AMPH-like stimulus effects, it is not necessarily inactive.

DOM-LIKE STRUCTURE-ACTIVITY RELATIONSHIPS

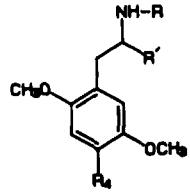
Aromatic Substituents

Substituents on the aromatic ring play a critical role in determining whether or not phenalkylamines possess DOM-like activity. Hallucinogenic activity is commonly associated with methoxy-substituted derivatives (Shulgin 1978); for this reason, much of this work has focused on these types of agents.

Methoxy-Substituted Derivatives. Phenalkylamines lacking aromatic substituents do not produce DOM-like stimulus effects. None of the three possible monomethoxy derivatives, 2-methoxy-(OMA), 3-methoxy-(MMA), or 4-methoxyphenylisopropylamine (PMA), produce DOM-like effects. Of the six dimethoxy analogs (DMAs) (i.e., 2,3-DMA, 2,4-DMA, 2,5-DMA, 2,6-DMA, 3,4-DMA, and 3,5-DMA), only the 2,4- and 2,5-dimethoxy derivatives 2,4-DMA and 2,5-DMA, respectively, are active. These two agents are essentially equipotent and are approximately one-tenth as potent as DOM. For purposes of comparison, the potencies of 2,5-DMA and DOM are 23.8 and 1.8 μmol/kg. Five trimethoxy analogs (TMAs) have been examined: 2,3,5-TMA is approximately one-third as potent as 2,5-DMA, and 2,3,4-TMA and 3,4,5-TMA are equipotent with 2,5-DMA. The other two, 2,4,5-TMA and 2.4.6-TMA, are about twice as potent as 2,5-DMA. None of the three possible tetramethoxy analogs has been investigated, and the pentamethoxy analog does not produce DOM-like stimulus effects. From these studies, it is apparent that the 2,4- and 2,5-dimethoxy substitution pattern plays an important role; certain 2.6-dimethoxy derivatives are also active, depending upon what substituents are present at the 4-position.

2,5-Dimethoxy Analogs. It should come as no surprise that methoxy groups at the 2- and 5-positions are important, when it is realized that DOM is a 2,5-dimechoxy-substituted derivative. Data for some representative 2,5-DMA analogs are provided in table 1. Removal of either one of the methoxy groups abolishes DOM-like stimulus effects. Introduction of a methyl group at the 4-position of 2,5-DMA, to produce DOM, enhances potency by more than an order of magnitude. Homologation of this alkyl group to ethyl (DOET) and *n*-propyl (DOPR) produces an increase in potency; further homologation to *n*-butyl (DOBU) decreases potency, and to amyl (DOAM) results in an agent that does not produce DOM-like stimulus effects. The relative potencies of these agents, as compared to 2,5-DMA, are: 2,5-DMA (1)<DOM (13)<DOET (27)<DOPR (43)>DOBU (7). Branching of this alkyl chain has varying effects. The isopropyl analog DOIP is eight times more potent than 2.5-DMA but is only about one-fifth as potent as its nonbranched counterpart DOPR. The tertiary butyl derivative DOTB does not produce DOM-like effects. In fact, it has been

TABLE 1. *Results of stimulus generalization studies using racemic DOM as a training drug*



Agent	Optical Isomer	R_4	R	R'	ED_{50} (µmol/kg)
2,5-DMA	(±)	H	H	CH_3	23.8
	(-)	H	H	CH_3	14.0
2,4,5-TMA	(±)	OCH_3	H	CH_3	13.7
DOM	(±)	CH_3	H	CH_3	1.8
	(-)	CH_3	H	CH_3	0.8
	(+)	CH_3	H	CH_3	6.9
N-Me DOM	(±)	CH_3	CH_3	CH_3	15.3
	(-)	CH_3	CH_3	CH_3	10.0
α-desMe DOM		CH_3	H	H	5.6
DOET	(±)	C_2H_5	H	CH_3	0.9
	(-)	C_2H_5	H	CH_3	0.3
	(+)	C_2H_5	H	CH_3	3.3
DOPR	(±)	nC_3H_7	H	CH_3	0.6
DOIP	(±)	iC_3H_7	H	CH_3	2.9
DOBU	(±)	nC_4H_9	H	CH_3	3.2
DOF	(±)	F	H	CH_3	5.8
DOC	(±)	C1	H	CH_3	1.2
DOI	(±)	I	H	CH_3	1.2
	(-)	I	H	CH_3	0.6
	(+)	I	H	CH_3	2.6
DOB	(±)	Br	H	CH_3	0.6
	(-)	Br	H	CH_3	0.3
	(+)	Br	H	CH_3	2.6
N-Pr DOB	(±)	Br	nC_3H_7	CH_3	13.4
α-desMe DOB		Br	H	H	2.2
4-OH 2,5-DMA	(±)	OH	H	CH_3	NSG
4-COOH 2,5-DMA	(±)	COOH	H	CH_3	NSG
DOTB	(±)	tC_4H_9	H	CH_3	NSG
DOAM	(±)	nC_5H_{11}	H	CH_3	NSG
DOBZ	(±)	CH_2-C_6H_5	H	CH_3	NSG

KEY: NSg=no stimulus generalization at the highest dose tested.

NOTE: Training drug=DOMHCl (1.0 mg/kg, IP) administered 15 minutes prior to testing. In test of stimulus generalization, a presession injection interval of 15 minutes was employed. ED_{50} values are given where stimulus generalization occured.

found that DOTB acts as a partial agonist and can antagonize the stimulus effects of DOM (Glennon 1987b).

Certain polar substituents at the 4-position of 2,5-DMA render the compounds inactive; for example, the 4-COOH and 4-OH derivatives do not produce DOM-like effects. On the other hand, 4-halogenated compounds result in relatively potent derivatives. The 4-fluoro derivative DOF is 4 times more potent than 2,5-DMA. whereas the 4-chloro (DOC) and 4-iodo (DOI) analogs are about 20 times more potent than 2,5-DMA. The most potent halogenated derivative is the 4-bromo analog DOB, which is about 40 times as potent as 2,5-DMA.

The location as well as the nature of these substituents is important. For example, moving the methyl group of DOM, or the bromo group of DOB, from the 4-position to the 3-position (to produce isoDOM and isoDOB, respectively) results in agents that do not produce DOM-like stimulus effects. IsoDOB (or SL7161). for example, produces saline-appropriate responding at 100 times the ED, dose of DOB.

2,4-Dimetboxy Analogs. 2,4-DMA is approximately equipotent with 2,5-DMA. Introduction of a 5-methyl or 5-bromo group, to produce 5-methyl-2,4-DMA and 5-bromo-2,4-DMA, results in active agents, but they are not significantly more potent than 2,4-DMA itself. It seems that the methyl and bromo substituents are tolerated at the 5-position, but they do not produce the increase in activity seen in the 2,5-DMA series.

Terminal Amine Substituents

A primary (i.e., unsubstituted) amine appears to be optimal for DOM-like activity. Simple N-monomethylation of DOM results in a tenfold decrease in potency. Larger N-alkyl substituents produce an even greater decrease in potency; for example, N-n-propyl DOB is approximately one-thirtieth as potent as DOB itself (Glennon et al. 1986b). Using animals trained to discriminate *R* (-)DQB from saline, racemic DOB is 10 times more potent than N-monomethyl DOB, which, in turn, is 10 times more potent than N,N-dimethyl DOB (Glennon et al. 1987). The quaternary analog N,N,N-trimethyl DOB iodide (QDOB) is inactive.

Alpha-Methyl Group

The u-methyl group is important, but not usually necessary for activity. For example, the α-desmethyl analogs of DOM and DOB are both about one-third as potent as their parent agents. The ademethylation of 3,4,5-TMA, to produce mescaline, results in a similar (i.e., 2.5-fold) decrease in activity. Although these α-desmethyl analogs produce stimulus effects similar to those of DOM, there is some evidence that the spectrum of effects produced by these agents, in rats and in humans, is not

necessarily identical with that (spectrum) of their parent compounds (Shulgin and Carter 1975; Glennon et al., in press).

Optical Isomers

Due to the presence of the a-methyl groups, these agents exist as optical isomers. Both isomers usually produce DOM-like effects, and the *R* (-)isomers constitute the eutomeric series. In this regard then, the effects of these agents are stereoselective, but not stereospecific. In general, the *R* (-)isomers are twice as potent as their racemates and about 5 to 8 times more potent than their *S* (+)enantiomers. Some representative data are provided in table 1.

AMPHETAMINE-LIKE STRUCTURE-ACTIVITY RELATIONSHIPS

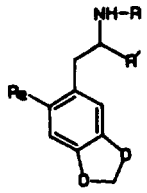
Aromatic Substituents

An unsubstituted aromatic ring appears to be optimal for AMPH-like stimulus effects. Using animals trained to discriminate 1.0 mg/kg of (+)amphetamine sulfate from saline (ED_{50}=1.8 µmol/kg), no aromatic-substituted derivative has yet been found to be more potent than AMPH itself. For example, each of the monomethoxy-substituted derivatives, i.e., OMA, MMA, and PMA, produce AMPH-appropriate responding but are 4 to 15 times less potent than AMPH itself (table 2). The (+)AMPH stimulus does not generalize to any of the above-mentioned DMAs or TMAs (or, for that matter, to any of the agents listed in table 1); however, several of these agents (notably 2,4-DMA, 2,5-DMA, 2,4,5-TMA, 2,4,6-TMA, and 3,4,5-TMA) result in partial generalization (40 to 50 percent AMPH-appropriate responding) suggesting that they may be capable of producing some AMPH-like activity in addition to their DOM-like effects (Glennon et al. 1985). The 4-OH derivative (parahydroxyamphetamine, or Paradrine), which is the O-desmethyl analog of PMA, produces saline-appropriate (2 percent drug-appropriate) responding at greater than 50 µmol/kg. The N-ethyl-3-trifluoromethyl derivative of AMPH, fenfluramine, produces saline-like effects at doses up to about 20 µmol/kg and disruption of behavior at doses greater than or equal to 24 µmol/kg. Complete reduction of the aromatic nucleus of AMPH does result in retention of activity, although potency is significantly decreased; that is, propylhexedrine produces AMPH-like stimulus effects (ED_{50}=15.5 µmol/kg).

Terminal Amine Substituents

In contrast to what was observed for DOM-like activity, N-monomethylation of AMPH-like agents does not decrease their AMPH-like character. Meth-AMPH (i.e., N-monomethylamphetamine) is slightly more potent than amphetamine; likewise, methcathinone (N-monomethylcathinone) is twice as potent as cathinone. N-methylation of DOM-like agents does not convert

TABLE 2. *Results of stimulus generalization studies using (+)amphetamine as a training drug*



Agent	Isomer	X	R_x	R	R'	ED_{50} (µmol/kg)
Amphetamine	(±)	H_2	H	H	CH_3	2.6
	(-)	H_2	H	H	CH_3	5.3
	(+)	H_2	H	H	CH_3	1.8
Methamphetamine	(±)	H_2	H	CH_3	CH_3	1.5
	(+)	H_2	H	CH_3	CH_3	1.2
Phenethylamine		H_2	H	H	H	NSG
Cathinone	(±)	0	H	H	CH_3	3.8
	(-)	0	H	H	CH_3	1.6
	(+)	0	H	H	CH_3	23.4
Methcathinone	(±)	0	H	CH_3	CH_3	1.8
N-OH AMPH	(±)	H_2	H	OH	CH_3	1.1
(+)N-Et AMPH	(+)	H_2	H	C_2H_5	CH_3	4.3
OMA	(±)	H_2	2-OCH_3	H	CH_3	38.7
MMA	(±)	H_2	3-OCH_3	H	CH_3	17.0
PMA	(±)	H_2	4-OCH_3	H	CH_3	9.5
PMMA	(±)	H_2	4-OCH_3	CH_3	CH_3	NSG
4-OH AMPH	(±)	H_2	4-OH	H	CH_3	NSG
Fenflummine	(±)	H_2	3-CF_3	C_2H_5	CH_3	NSG
3,4-DMA	(±)	H_2	3,4-di OCH_3	H	CH_3	NSG
N-Me 3,4-DMA	(±)	H_2	3,4-di OCH_3	CH_3	CH_3	NSG
2,4-DMA	(±)	H_2	2,4-di OCH_3	H	CH_3	NSG
N-Me 2,4-DMA	(±)	H_2	2,4-di OCH_3	CH_3	CH_3	NSG
2,5-DMA	(±)	H_2	2,5di OCH_3	H	CH_3	NSG
N-Me 2,5-DMA	(±)	H_2	2,5-di OCH_3	CH_3	CH_3	NSG

KEY: NSG=no stimulus generalization at the highest dose tested.

NOTE: Rats trained to dircriminate (+)amphetamine sulfate (1.0 mg/kg) from saline administered 15 minuted prior to testing.

them to AMPH-like agents; for example, see N-Me 2,4-DMA and N-Me 2,5-DMA (table 2). Homologation of the methyl to an ethyl group results in retention of AMPH-like activity, although potency is somewhat reduced;

for example, (+)N-Et AMPH is 2.5 times less potent than (+)AMPH itself. Although there have been no systematic investigations of N-alkylation, certain AMPH analogs bearing larger substituents are active. Mefenorex, the N-(3-chloro-n-propyl) analog of AMPH, produces saline-appropriate behavior at about 5.5 µmol/kg and disruption of behavior at 6 µmol/kg.The N-hydroxy analog of AMPH (i.e., N-OH AMPH), a metabolite of AMPH, also produces AMPH-like effects and is about twice as potent as AMPH (table 2).

Alpha-Methyl Group

Removal of the a-methyl group of AMPH results in phenethylamine (PEA). PEA does not produce AMPH-like effects. Likewise, removal of the a-methyl group of cathinone, resulting in α-desmethylcathinone, also results in an agent that does not produce AMPH-like stimulus effects. Huang and Ho (1974a) have demonstrated that pretreatment of the animals with a monoamine oxidase inhibitor prior to administration of PEA does lead to stimulus generalization, suggesting that the adesmethyl analogs may simply lack protection from metabolism.

Beta-Substituents

Very few ~-substituted analogs of AMPH have been investigated. Ephedrine, for example, produces weak AMPH-like activity (Huang and Ho 1974b). (+)Norpseudoephedrine (cathine) also produces AMPH-like stimulus effects. The oxidized analogs of norephedrine and ephedrine, cathinone and methcathinone, respectively, however, are potent AMPH-like agents (table 2).

Optical Isomers

Both optical isomers of AMPH are active (Schechter 1978). In general, for the few isomeric pairs that have been examined, the *S* isomers of AMPH-like agents are slightly more potent than the racemates and about 3 times more potent than the *R* isomers (Young and Glennon 1986). *S*(+)AMPH, for example, is 3 times more potent than *R*(-)AMPH (table 2); *S*(-)cathinone is 2.5 times more potent than racemic cathiione, but (unexpectedly) is nearly 15 times more potent than *R*(+)cathinone.

Miscellaneous Analogs

Certain agents with AMPH-related structures also produce AMPH-like stimulus effects. Agents in which the terminal amine has been incorporated into a cyclic structure, such as methylphenidate (Huang and Ho 1974b D'Mello 1981), phenmetrazine, and phendimetrazine, are active. These agents might be considered as N-alkyl β-substituted phefialkylamines. Aminorex is another agent that falls into this category and is essentially equipotent with AMPH.

METHYLENEDIOXY-SUBSTITUTED PHENALKYLAMINES

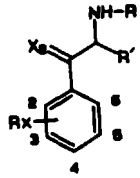
Methylenedioxy-substituted phenalkylamines are considered separately, because it has been shown that the parent 3,4-methylenedioxy analog of AMPH, MDA, is capable of producing both DOM-like and AMPH-like stimulus effects. Its ED, value in DOM-trained rats is 7.8 µmol/kg and in (+)AMPH-trained rats, 10.6 µmol/kg. The DOM-like properties reside primarily with the *R* (-)isomer (ED_{50}=3.8 µmol/kg), whereas the AMPH-like activity resides with the *S* (+)isomer (ED_{50}=4.2 µmol/kg) (figures 2 and 3). To this extent, 3,4-MDA is not a particularly potent agent; it is approximately one-sixth as potent as (+)AMPH and less than one-third as potent as DOM. A positional isomer of 3,4-MDA. 2,3-MDA, produces neither DOM- nor AMPH-like stimulus effects. The 2-methoxy analog of 3,4-MDA (i.e., 2-methoxy 4,5-MDA or MMDA-2) produces weak DOM-like effects (ED_{50}=13.7 µmol/kg), but does not produce AMPH-like stimulus effects.

3,4-MDA is unique. Not only does it produce both types of effects, but it seems to conflict with some of the above-mentioned SARs. For example, aromatic-substituted phenalkylamines such as the 3-methoxy and 4-methoxy derivatives MMA and PMA arc only weak AMPH-like agents, and the 3.4-dimethoxy analog 3,4-DMA (which is structurally very similar to 3,4-MDA) does not produce AMPH-like effects. The 3-OH, 4-OMe, and the 3-OMe 4-OH analogs of amphetamine are also inactive. Thus, it is surprising that 3,4-MDA possesses AMPH-like character. Likewise, neither MMA, PMA, nor 3,4-DMA produce DOM-like effects; yet 3,4-MDA does. 2-Methoxy 4,5-MDA (MMDA-2) and 2,4,5-TMA share a common substitution pattern; interestingly, these agents are essentially equipotent in producing DOM-like stimulus effects. Table 3 displays selected results.

CONTROLLED SUBSTANCE ANALOGS ("DESIGNER DRUGS")

One application of SARs is to make predictions concerning new agents. Assuming that the new agents are producing one of the above-mentioned effects, it should be possible to make approximate predictions of both activity and potency. Over the past decade, several new agents have appeared, and their activities and/or potencies have been consistent with these SARs. Some of these agents have been mentioned. Also encountered were some agents that do not fit the foregoing SAR; it is probably worthwhile considering these agents in depth. For example, PMMA, the N-monomethyl analog of PMA, should produce AMPH-like effects with a potency several times that of PMA itself. In fact, PMMA produces neither AMPH-like nor DOM-like effects. The animals' behavior, however, was disrupted at very low doses (<1 µmol/kg) suggesting that it may produce a central effect that is other than (or in addition to) AMPH-like or DOM-like.

TABLE 3. *Results of stimulus generalization studies with MDA analogs*



Agent	Isomer	R_2	R	R'	ED, Values (µmol/kg) AMPH-Like	DOM-Like
3,4-MDA (MDA)	(±)	H	H	CH_3	10.6	7.8
	(-)	H	H	CH_3	NSG	3.7
	(+)	H	H	CH_3	4.2	NSG
HPA		H	H	H	NSG	NSG
2-OMe 4,5-MDA	(±)	OCH_3	H	CH_3	NSG	13.7
N-Me 2-OMe 4,5MDA	(±)	OCH_3	CH_3	CH_3	NSG	-
MDMA	(±)	H	CH_3	CH_3	7.1	NSG*
	(-)	H	CH_3	CH_3	NSG	NSG*
	(+)	H	CH_3	CH_3	2.6	NSG*
MDE	(±)	H	C_2H_5	CH_3	NSG	NSG
	(-)	H	C_2H_5	CH_3	NSG	NSG
	(+)	H	C_2H_5	CH_3	NSG	NSG
MDP	(±)	H	C_3H_7	CH_3	NSG	NSG
N-OH MDA	(±)	H	OH	CH_3	NSG	NSG

*Partial generalization (i.e., 40 to 55 percent drug-appropriate responding, followed, at slightly higher doses, by disruption of behavior. NSG=no stimulus generalization at the highest dose tested.

NOTE: AMPH-like rats were trained to discriminate 1.0 mg/kg of (+)amphetamine sulfate from saline; DOM-like rats were trained to discriminate 1.0 mg/kg of DOM-HC1 from saline.

The N-monomethyl analog of 3,4-MDA is MDMA (XTC, "Ecstasy," "Adam"). It would be anticipated that N-monomethylation of MDA would reduce DOM-like character by at least an order of magnitude, simuitaneously enhancing the AMPH-like character. Thus, the AMPH stimulus should generalize to the racemate and to the *S* (+)isomer (with the latter being the more potent, and somewhat more potent than *S*(+)MDA), and the *R* (-)isomer might have, at best, some weak DOM-like character. Indeed, the (+)AMPH stimulus generalizes to racemic MDMA (ED_{50}=7.1 µmol/kg) (figure 4) and to *S*(+)MDMA (ED_{50}=2.6 µmol/kg), but not to *R*(-)MDMA.

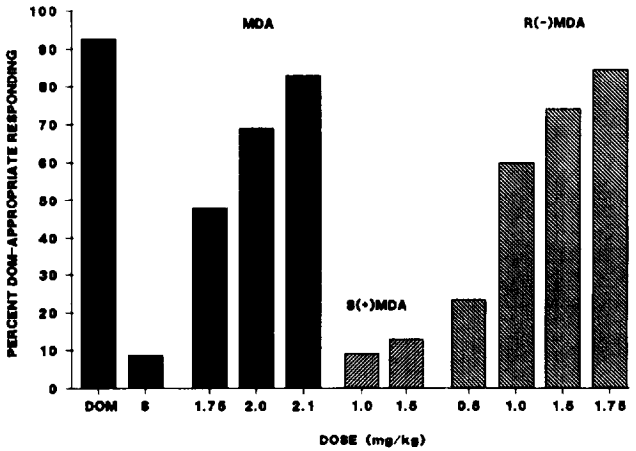


FIGURE 2. *The effects of racemic 3,4-MDA (MDA) and its optical isomers in rats trained to discriminate DOM from saline*

KEY: DOM=effect produced by the training dose, 1 mg/kg. of DOM; S=effect produced by 1 mL/kg of 0.9 percent saline.

NOTE: Doses of S(+)MDA greater than 1.5 mg/kg resulted in disruption of behavior. Results not shown for all doses evaluated. Where stimulus generalization did not occur, result of highest nondisruptive dose of test compounds is shown; slightly higher doses produced disruption of behavior.

More recently, others (Evans and Johanson 1986; Kamien et al. 1986) have published similar results with racemic MDMA. The DOM stimulus does not generalize to racemic MDMA or to either isomer. To this extent, the results appear to be consistent with established SARs.

MDE (MDEA, "Eve") is the N-ethyl analog of MDA. SARs would suggest that this agent should possess little, if any, DOM-like character and that it should be a rather weak AMPH-like agent, Interestingly, neither the racemate (figure 4) nor either optical isomer (figure 5) produces (+)AMPH-appropriate responding. As expected, DOM stimulus generalization does not occur with racemic MDE or with either of its optical isomers (figure 6). Another inconsistency is encountered with the N-hydroxy analog of MDA (i.e., N-OH MDA). Because N-hydroxylation of AMPH has relatively little effect on its stimulus properties, it was anticipated that N-OH MDA might behave in a manner similar to that of MDA. Figure 7 shows that N-OH MDA produces neither AMPH-like nor DOM-like stimulus effects. It should be noted, however, that the optical isomers of N-OH MDA have not yet been examined.

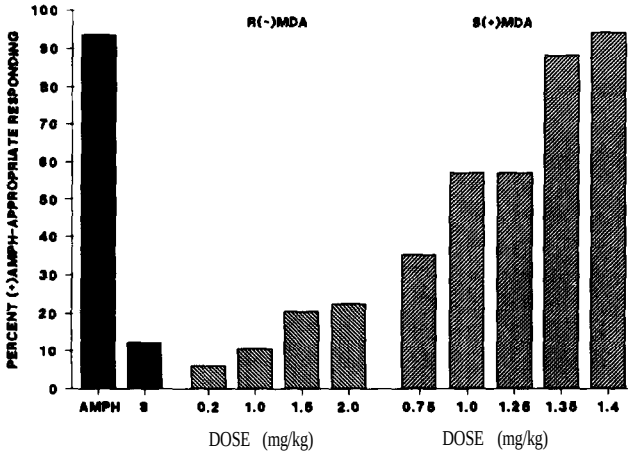


FIGURE 3. *Effect of* R*(-)MDA and* S*(+)MDA in rats trained to discriminate* S*(+)AMPH from saline*

KEY: AMPH=effect of the training dose. 1 mg/kg. of S(+)amphetamine sulfate; S=the effect of 1 mL/kg of 0.9 percent saline.

NOTE: Results not necessarily shown for all doses that were examined. Where stimulus generalization did not occur, result of highest nondisruptive dose is shown; evaluation of a slightly higher dose resulted in disruption of behavior.

At this point, the unexpected results cannot be readily explained with PMMA, MDE, or N-OH MDA. This is particularly confounding in view of the report that MDMA and MDE apparently produce similar psychopharmacological effects in humans (Braun et al. 1980). There are several possible explanations: (1) these agents may produce effects in rats that are different from those produced in humans; (2) these agents may produce in rats a central effect that somehow masks or obscures AMPH-like effects that might have otherwise been observed at higher doses had disruption of behavior not occurred at lower doses; and (3) some of these agents might be capable of producing a stimulus effect distinct from those produced by either AMPH or DOM (Glennon et al. 1988). The recent results of Oberlender and Nichols (1988) would tend to support the latter possibility.

To gain further insight into the stimulus properties of these agents, a group of rats was trained to discriminate MDA (1.5 mg/kg) from saline. Consistent with the generalization results described above, the MDA-trained animals recognized both racemic AMPH and DOM (table 4). MDA stimulus generalization also occurred with both isomers of MDA, with *S*(+)MDA (ED_{50}=2.4 µmol/kg) being about twice as potent as *R*(-)MDA

TABLE 4. *Results of stimulus generalization studies using rats trained to discriminate 1.5 mg/kg* of racemic *MDA from saline*

Agent	Optical Isomer	ED_{50} (µmol/kg)
MDA	(±)	3.0
	(-)	5.5
	(+)	2.4
AMPH	(±)	7.7
DOM	(±)	2.5
MDMA	(±)	4.2
3,4-DMA	(±)	23.2
2,3-MDA	(±)	13.4
Cocaine	(+)	17.3
LSD	(+)	0.07

(ED_{50}=5.5 µmol/kg). Because MDA produces both AMPH-like and DOM-like stimulus effects, it would be expected that MDA-trained animals would recognize both cocaine and LSD, this was found to be the case (Glennon and Young 1984a). Interestingly, the MDA stimulus also generalized to 3,4-DMA and 2,3MDA, agents to which neither the AMPH or DOM stimulus generalizes. These results suggest that MDA is indeed producing both AMPH-like and DOM-like effects and that it may also produce some other stimulus effect.

Next trained was a group of rats to discriminate racemic MDMA from saline. It was found that MDMA-trained animals (MDMA, ED_{50}=2.2 µmol/kg) recognize both *S*(+)MDMA (ED_{50}=1 µmol/kg) and *R*(-)MDMA (ED_{50}=4.3 µmol/kg). Thus, both isomers of MDMA appear to be active, with *S*(+)MDMA being 4 times more potent than *R*(-)MDMA (Glennon et al. 1986c). More recently, Schechter (1987) has reported an enantiomeric potency ratio of about 2, whereas Oberlender and Nichols (1988) obtained a ratio of 2.6. All three studies agree that the *S* (+)isomer is the more active isomer, and two of the three studies find that it is twice as potent as the racemate. Schechter (1987), on the other hand, has found that the racemate is twice as potent as the *S* (+)isomer.

It is probably important to note that although there may be differences between the effects produced by MDMA and MDE, there are also significant similarities. For example, preliminary data using MDMA-trained animals suggest that racemic MDMA and MDE produce similar stimulus

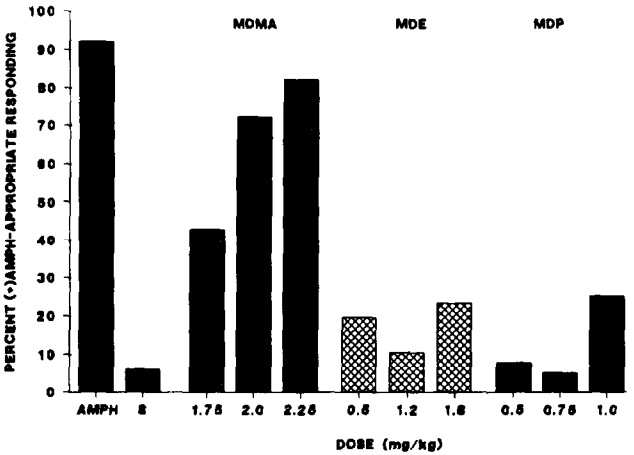


FIGURE 4. *Effect of racemic MDMA, MDE, and MDP in animals trained to discriminate (+)AMPH from saline*

KEY: AMPH=effect of the training dose., 1 mg/kg, of S(+)amphetamine sulfate; S=the effect of 1 mL/kg of 0.9 percent saline.

NOTE: Results not necessarily shown for all doses that were examined. Where stimulus generalization did not occur, result of highest nondisruptive dose is shown; evaluation of a slightly higher dose resulted in disruption of behavior.

effects, with MDE being slightly less potent than MDMA. At 8.2 µmol/kg. MDE produces stimulus effects comparable to those of 6.5 µmol/kg of MDMA. These results are consistent with those of Boja and Schechter (1987), who used animals trained to discriminate MDE from saline. On the other hand, whereas both MDMA and MDE are significantly less potent than (+)AMPH in increasing locomotor activity in mice, *S*(+)MDMA and *S*(+)MDE are about an order of magnitude more potent than their *R* (-)enantiomers, and S(+)MDMA is at least several times more potent than *S*(+)MDE (Patrick and Glennon, unpublished data).

Several recent reports allay fears that some progress is being made. For example. whereas MDA (Glennon and Young 1984b; Evans and Johanson 1986; Kamien et al. 1986). *S*(+)MDA (Glennon and Young 1984b), MDMA and/or *S*(+)MDMA (Glennon and Young 1984b; Evans and Johanson 1986; Kamien et al. 1986; Glennon et al. 1988) produce AMPH-like effects, *S*(+)MDA produces cocaine-like effects (Broadbent et al. 1987), and although MDMA-trained animals recognize *S*(+)AMPH (Oberlender and Nichols 1988), there are additional reports that AMPH-trained animals fail

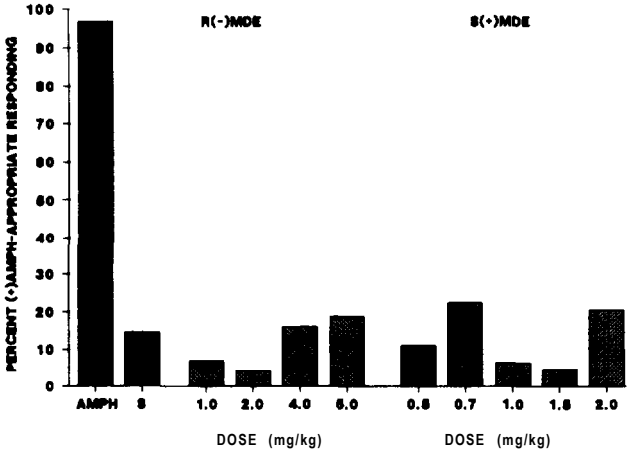


FIGURE 5. *Effect of* R*(-)MDE and* S*(+)MDE in animals trained to discriminate (+) AMPH from saline*

KEY: AMPH=effect of the training dose, 1 mg/kg, of S(+)amphetamine sulfate S=the effect of 1 mL/kg of 0.9 percent saline.

NOTE: Results not necessarily shown for all doses that were examined. Where stimulus generalization did not occur, result of highest nondisruptive dose is shown; evaluation of a slightly higher dose resulted in disruption of behavior.

to recognize *S*(+)MDA (Broadbent et al. 1987). MDMA, *S*(+)MDMA. and *R*(-)MDMA (Oberlender and Nichols 1988). Furthermore, Appel and coworkers have reported in one study that LSD-trained animals recognize both isomers of MDA (Broadbent et al. 1987) and, in another study, that LSD-trained animals recognize *R*(-)MDA but not *S*(+)MDA, *R*(-)MDMA, or *S*(+)MDMA (Callahan and Appel 1987). Consistent with results in DOM animals, Nichols and coworkers (1986) have found that LSD-trained animals recognize racemic MDA and *R*(-)MDA. In the latter study, half the animals tested also recognized *R*(-)MDMA. and 78 percent of a group of rats trained to discriminate MDMA from saline selected the drug-appropriate lever when administered LSD. However, *R*(-)MDA, *S*(+)MDA, *R*(-)MDMA, and *S*(+)MDMA all produced drug-appropriate responding in rats trained to discriminate mescaline from saline (Callahan and Appel 1987). These inconsistencies might be due to procedural differences, or they might be of greater significance. It is believed that *R*(-)MDA produces primarily, but not exclusively, DOM-like (or hallucinogenic) effects, and that *S*(+)MDA produces primarily, but not exclusively, AMPH-like effects. N-monomethylation of MDA enhances AMPH-like character and decreases DOM-like properties.

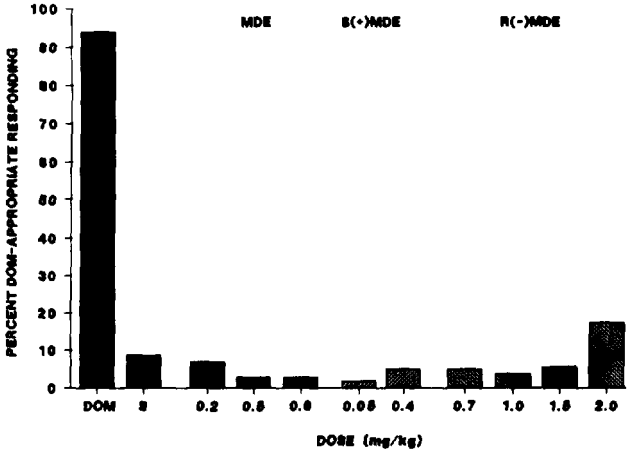


FIGURE 6. *Effect of MDE and its optical isomers in rats trained to discriminate DOM from saline*

KEY: DOM=effect produced by the training dose, 1 mg/kg of DOM; S=effect produced by 1 mL/kg of 0.9 percent saline.

NOTE: Doses of S(+)MDA (greater than 1.5 mg/kg resulted in disruption of behavior. Results not shown for all doses evaluated. Where stimulus generalization did not occur, result of highest nondisruptive dose of test compounds is shown; slightly higher doses produced disruption of behavior.

Evidence further suggests that MDMA (possibly MDA), and particularly MDE and MDP, can produce effects that are distinct from (or that are in addition to, but mask) AMPH-like and/or DOM-like effects.

Recent work shows that, in rodents, MDMA is metabolized, at least in part, to MDA, and that racemic MDMA is preferentially metabolized to *S*(+)MDA (Fitzgerald et al. 1987). The extent to which MDMA metabolites might contribute to the stimulus properties of MDMA is unknown at this time. Because *S*(+)MDA is capable of producing AMPH-like stimulus effects, involvement of this metabolite might explain some of the different results reported for MDMA (particularly if different animal species and various presession injection intervals were employed). In contrast, certain other potential metabolites of MDMA, such as 3-hydroxy-PMA, 4-hydroxy-MMA, 3,4-dihydroxy-AMPH (α-methyldopamine), N-methyl-3-hydroxy-PMA, N-methyl-4-hydroxy-MMA, N-methyl-3,4-dihydroxy-AMPH (N-methyl-α-methyldopamine) do not produce AMPH-like stimulus effects, but may be capable of producing other, distinct types of central activity or may somehow interfere with potential AMPH-like effects.

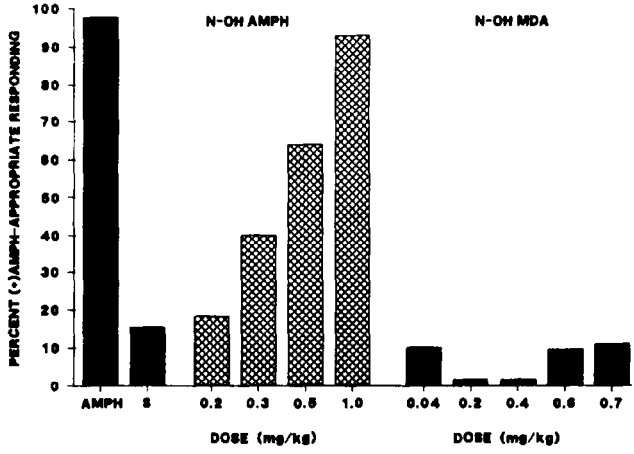


FIGURE 7. *Effect of N-OH AMPH and N-OH MDA in rats trained to discriminate (+)amphetamine from saline*

KEY: AMPH=effect of the training dose, 1 mg/kg. of S(+)amphetamine sulfate; S=the effect of 1 mL/kg of 0.9 percent saline.

NOTE: Results not necessarily shown for all doses that were examined. Where stimulus generalization did not occur, result of highest nondisruptive dose is shown; evaluation of a slightly higher dose resulted in disruption of behavior.

CONCLUSION

The drug discrimination paradigm is a powerful tool for studying centrally acting agents of the phenalkylamine type. It has been used to classify a large number of agents as being either AMPH-like or DOM-like, and it allows for the formulation of SARs. Though not discussed here, drug discrimination studies have proven invaluable in understanding the mechanisms of action of many of these agents (Glennon et al. 1986a; Young and Glennon 1986; Glennon 1988). The SAR can also be used to predict the activity (AMPH-like or DOM-like) and potency of novel agents. Two significant exceptions to established SARs have been encountered PMMA and the MDA analogs. Findings with PMMA were wholly unexpected. MDA analogs probably represent a special case; because no methylenedioxy analogs were included in the data set used to formulate the initial SARs, it may not be wholly valid to attempt extrapolation to these types of agents. Nevertheless, there are instances where the SARs correctly predict the activity and potency of certain analogs (e.g., MMDA-2, MDMA). However, other MDA analogs (i.e., N-OH MDA, MDE, MDP) seemingly lack all regard for the established SARs. Although differences in

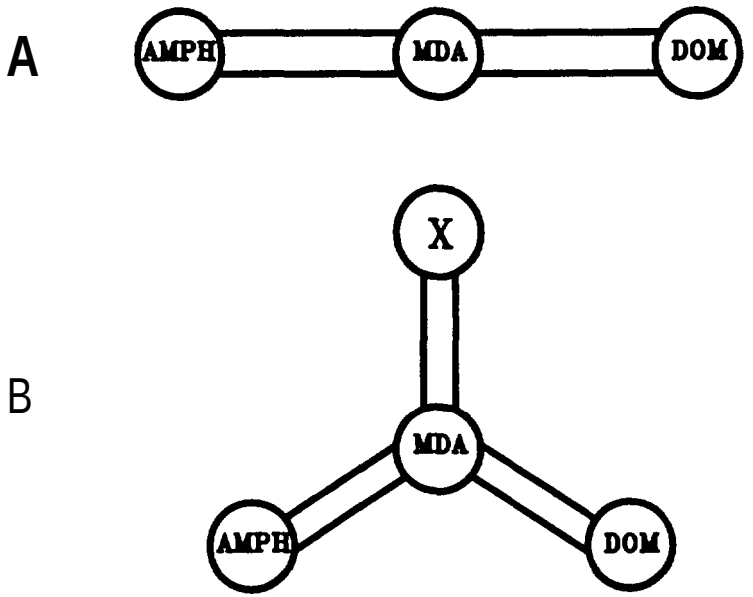


FIGURE 8. *Phenalkylamine analogs appear to produce central stimulus effects along AMPH-like to DOM-like continuum, depending upon the substituent groups present*

NOTE: (A.) MDA produces both types of stimulus effects. (B.) Trifurcated model is presented to account for a possible third, as yet undefined, type of central effect. Certain phenalkylamines may exert effects better described by the MDA/X component of this model than by either pure AMPH-like or DOM-like action.

metabolism and distribution may account for some of the observed results, it is entirely possible that some of these agents might also produce a unique effect that is neither AMPH-like nor DOM-like. Future drug discrimination studies, using the MDA analogs as training drugs, should be of immense benefit in understanding their stimulus effects.

Phenalkylamines are capable of producing a wide variety of pharmacological effects; prominent among the central stimulus effects produced by these agents are AMPH-like effects and DOM-like (or DOB-like) effects. Nearly a decade ago, the author proposed that such agents exist along an AMPH/DOM continuum and that the nature and location of pendent substituents determine where along this continuum an agent may lie (Glennon et al. 1980). It seems likely that MDA is positioned somewhere near the center of this continuum, because it produces both AMPH-like and DOM-like effects. Current evidence suggests the need for a revised model to explain the activity of MDE and MDP and the finding that 2,3-MDA and 3,4-DMA produce MDA-like, but not AMPH-like or DOM-like stimulus

effects. Certain of these agents may produce non-AMPH/non-DOM-like effects (with or without a certain amount of residual AMPH-like or DOM-like character); to account for this, a trifurcated continuum as shown in figure 8 is proposed. Agents such as MDE and MDP may exist somewhere along the MDA/X segment of this new model. The presence of the methylenedioxy group may not be a prerequisite for agents to exist along this arm of the model if, for example, agents such as PMMA can be shown to produce effects similar to those of MDE. In contrast, the amine substituents may play an important role. Obviously, additional studies will be necessary to support this working model. The model, as simplistic as it may be, accounts for the fact that certain of these agents possess some AMPH-like or DOM-like character but, at the same time, do not seem to follow the established SAP. The "X-like" activity (which could, in reality, consist of several different actions) may be a consequence of direct or indirect actions on dopamine and/or serotonin receptors (or populations of these receptors not normally involved in the actions of AMPH or DOM) or may represent actions at entirely different types of receptors.

DISCUSSION

COMMENT: I was surprised by the results with the N-hydroxy compounds, because a number of years ago N-hydroxy-p-toluylamphetamine was studied, and it was found that it was identical to ptoluylamphetamine in its properties because it was actually rapidly and essentially quantitatively converted to p-toluylamphetamine. You are finding that the N-hydroxy analog of MDMA is not MDMA-like in its properties. These data suggest that they certainly are not metabolized in a similar way, perhaps.

RESPONSE: I did not show that the N-hydroxy analog of MDA is not MDMA-like. I showed that it is not amphetamine-like.

COMMENT: That makes it not MDMA-like.

RESPONSE: You can extrapolate. I have problems with those extrapolations.

COMMENT/QUESTION: I was not using MDMA-like in the sense that you were using it--as a substitute. I am simply saying it did not have the pharmacologic effect that MDMA had; namely, substitution for amphetamine, which obviously must mean that the N-hydroxy compound is not converted to MDMA to the same extent at least as the p-toluylamphetamine analog was. I would like to know if you have any information about the metabolism of those N-hydroxy compounds.

RESPONSE/QUESTION: None whatsoever. We are looking at the metabolism of some of the other compounds, but we have not looked at the

N-hydroxy. Has the N-hydroxy MDA been identified as a metabolite of MDA from the earlier studies?

ANSWER: Not that I can remember.

RESPONSE: We have not looked at that at all. But it is surprising. I expected to see either hydroxylation or dehydroxylation, so I expected to see similar activities. But this is what we see. If you compare the activities on a milligram per kilogram basis, the N-hydroxy amphetamine appears to be equipotent. However, when you look at the molecular weights (it is a different salt), it is in fact twice as potent. I cannot explain that.

QUESTION: With respect to the N-hydroxy MDA, have you done a timecourse to see whether at longer times you might pick it up if it is a metabolic induction?

ANSWER: No, we have not. It is an idea.

QUESTION: I noticed that my group is the major one that disagrees with the amphetamine-like activity of MDMA. And when you look at the MDE and MDP you lose that. Is it possible that this MDMA-like activity is really an artifact? That is, that the rats are saying it seems to be amphetamine-like but, in fact, it really is not. And when you go ahead and put the ethyl or propyl, you do not see the amphetamine-like activity because that simply is not what it is?

ANSWER: Obviously no one knows what the rats are thinking. My opinion, based on what we have done so far, is that MDE and MDP may be doing something different. We may have a third wheel on this continuum, it may be a three-way continuum with MDA in the middle. Maybe there is a third kind of effect that MDA is capable of producing, but this is grossly overshadowed by its amphetamine-like or DOM-like activity.

If we start making analogs of MDA like the N-methyl, that moves it a little off center. It still retains some amphetamine-like activity. It may, at high doses, have DOM-like activity. We certainly do not see it. And then we have this third type of effect if we go even farther out to the ethyl homolog or to the types of compounds that you are making. You may have now gotten far enough from center that these compounds no longer have the amphetamine-like or the DOM-like character. But what we see with MDMA is that it is amphetamine-like.

QUESTION: Where does parachloroamphetamine fit in here?

ANSWER: We have never looked at parachloroamphetamine itself.

QUESTION: Substitution of lipophilic moieties on the phenyl ring of DOM makes the compounds more potent. Substitution of ionic-type moieties. like hydroxyl anions, makes them less potent. Is that a good generalization, that making the phenyl ring more lipophilic makes the compounds more potent in the DOM series?

ANSWER: No. There appears to be an optimal potency beyond which the compounds are no longer active as agonists but can, in fact, act as antagonists. So we have analogs of DOM that can antagonize the effects of DOM, because we have passed this optimal lipophilicity. The idea of lipophilicity at the four position is not new, and a number of investigators have looked at this over the years with regard to hallucinogenic activity.

Recently we have been looking at it with regard to binding at 5-HT_2 sites. And we see this correlation fits very well. As we get up to a certain point though, it stops. It appears that, in terms of discrimination and in humans, the propyl compound appears to be optimal. Once we get beyond that, lipophilicity continues to increase, 5-HT_2 receptor affinity continues to increase. The compounds start decreasing in potency and, in fact, they become inactive. So it may be that some of these are partial agonists, and ultimately we get out to antagonists of DOM. So it is not a strictly linear relationship.

QUESTION: Is there any evidence that a common effect of amphetamine and MDMA is mediated through a common biochemical mechanism; for example, antagonism studies in haloperidol?

ANSWER: No, we have not done anything in that regard in terms of drug discrimination.

QUESTION: You seemed to have looked through all of the various substituents in your amphetamine structure, with one exception. You did not touch the benzene ring itself. What would happen if you saturate the benzene ring and make a saccharide derivative of amphetamine?

ANSWER: It retains amphetamine-like activity.

RESPONSE: This is what, propylhexedrine? We have looked at propylhexedrine, and it does retain amphetamine-like activity, but it is less potent. In rats trained to discriminate 1.5 mg/kg of racemic MDMA from saline (ED_{50}=0.76 mg/kg), the ED_{50} values for stimulus generalization to MDE and N-OH MDA are 0.73 and 0.47 mg/kg, respectively (Glennon and Misenheimer, unpublished observations).

REFERENCES

Boja, J.W., and Schechter, M.D. Behavioral effects of N-ethyl-3,4-methylenedioxyamphetamine (MDE; "Eve"). *Pharmacol Biochem Behav* 28:153-156, 1987.

Braun, U.; Shulgin, A.T.; and Braun, G. Prufung auf zentrale aktivitat und analgesie von n-substitutierten analogen des amphetamin-derivates 3,4-methylenedioxyphenylisopropylamin. *Drug Research* 30:825-830, 1980.

Broadbent, J.; Michael, E.K.; Ricker, J.H.; and Appel, J.B. A comparison of the discriminative stimuli of (+) and (-) 3,4-methylenedioxyamphetamine (MDA) with those of hallucinogenic and stimulant drugs. *Abstr Soc Neurosci* 13:1720, 1987.

Callahan, P.M., and Appel, J.B. Differences in the stimulus properties of 3,4-methylenedioxyamphetamine (MDA) and N-methyl-1-(3,4-methylenedioxyamphetamine) MDMA in animals trained to discriminate hallucinogens from saline. *Abstr Soc Neurosci* 13:1720, 1987.

D'Mello, G.D. Comparison of some behavioral effects of and electrical brain stimulation of the mesolimbic dopamine system in rats. *Psychopharmacology (Berlin)* 75:184-192, 1981.

Evans, SM., and Johanson, C.E. Discriminative stimulus properties of 3,4-methylenedioxymethamphetamine and 3,4-methylenedioxyamphetamine in pigeons. *Drug Alcohol Depend* 18:159-164, 1986.

Fitzgerald, R.; Blanke, R.V.; Namsimhachari, N.; Glennon, R.A.; and Rosecrans, J.A. Identification of 3,4-methylenedioxyamphetamine (MDA) as a major urinary metabolite of 3,4-methylenedioxymeth-amphetamine (MDMA). Presented at the Committee on Problems of Drug Dependence Meeting, Philadelphia, PA, June 1987.

Glennon, R.A. Discriminative stimulus properties of phenylisopropylamine derivatives. *Drug Alcohol Depend* 17:119-134, 1986.

Glennon, R.A. Psychoactive phenylisopropylamines. In: Meltzer, H.Y., ed. *Psychopharmacology: The Third Generation of Progress.* New York Raven Press, 1987a. pp. 1627-1634.

Glennon, R.A. Synthesis and evaluation of amphetamine analogs. Proceedings of the Joint WHO/Drug Enforcement Administration Conference on Controlled Substance Analogs. Rabat, Morocco, September, 1987b.

Glennon, R.A. Site-selective serotonin agonists as discriminative stimuli. In: Colpaert. F.C., and Balster, R.L., eds. *Transduction Mechanisms of Drug Stimuli.* Berlin: Springer-Verlag, 1988. pp. 16-31.

Glennon, R.A., and Young, R. MDA: An agent that produces stimulus effects similar to those of 3,4-DMA, LSD and cocaine. *Eur J Pharmacol* 99:249-250, 1984a

Glennon, R.A., and Young, R. Further investigation of the stimulus properties of MDA. *Pharmacol Biochem Behav* 20:501-505, 1984b.

Glennon, R.A.; Liebowitz, S.M.: and Anderson, G.M. Serotonin receptor affinities of psychoactive phenalkylamine analogues. *J Med Chem* 23:294-299, 1980.

Glennon, R.A.; Rosecrans, J.A.; and Young, R. Drug-induced discrimination: A description of the paradigm and a review of its specific application to the study of hallucinogenic agents. *Med Res Rev* 3:289-340, 1983.

Glennon, R.A.; Young, R.; and Hauck, A.E. Structure-activity studies on methoxy-substituted phenylisopropylamines using drug discrimination methodology. *Pharmacol Biochem Behav* 22:723-729, 1985.

Glennon, R.A.; Titeler, M.; and Young, R. Structure-activity relationships and mechanism of action of hallucinogenic agents based on drug discrimination and radioligand binding studies. *Psychopharmacol Bull* 22:953-958, 1986a.

Glennon, R.A.; McKenney, J.D.; Lyon, R.A.; and Titeler, M. 5-HT_1 and 5-HT_2 binding characteristics of 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane analogues. *J Med Chem* 29:194-199, 1986b.

Glennon, R.A.; Titeler, M.; Lyon, R.A.; and Yousif, M. MDMA ("Ecstasy"): Drug discrimination and brain binding properties. *Abstr Soc Neurosci* 12:919, 1986c.

Glennon, R.A.: Titeler, M.; Seggel, M.R.; and Lyon, R.A. N-methyl derivatives of the 5-HT_2 agonist 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane. *J Med Chem* 30:930-932, 1987.

Glennon, R.A.; Yousif, M.; and Patrick, G. Stimulus properties of 1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDA) analogs. *Pharmacol Biochem Behav* 29:442-449, 1988.

Glennon, R.A.; Titeler, M.; and Lyon, R.A. A preliminary investigation of the psychoactive agent 4-bromo-2,5-dimethoxyphenethylamine: A potential drug of abuse. *Pharmacol Biochem Behav.* in press.

Huang, J.T., and Ho, B.T. The effect of pretreatment with iproniazid on the behavioral activities of β-phenethylamine in rats. *Psychopharmacologia* [Berlin] 35:77-81, 1974a.

Huang, J.T., and Ho, B.T. Discriminative stimulus properties of *d*-amphetamine and related compounds in rats. *Pharmacol Biochem* Behav 2:569-673, 1974b.

Kamien, J.B.; Johanson, C.E.; Schuster, C.R.; and Woolverton, W.L. The effects of (±)methylenedioxymethamphetamine and (±)methylenedioxyamphetamine in monkeys trained to discriminate (+)amphetamine from saline. *Drug Alcohol Depend* 18:139-147, 1986.

Nichols, D.E.; Hoffman, A.J.; Oberlender, R.A.; Jacob, P., III; and Shulgin, A.T. Derivatives of 1-(1,3-benzodioxol-5-yl)-2-butaneamine: Representatives of a novel therapeutic class. *J Med Chem* 29:2009-2015, 1986.

Oberlender, R., and Nichols, DE. Drug discrimination studies with MDMA and amphetamine. *Psychopharmacology (Berlin)* 95:71-76, 1988.

Schechter, M. Stimulus properties of *d*-amphetamine as compared to *l*-amphetamine. *Eur J Pharmacol* 47:461-464, 1978.

Schechter, M. MDMA as a discriminative stimulus: Isomeric comparisons. *Pharmacol Biochem Behav* 27:41-44, 1987.

Shulgin, A.T. Psychotomimetic drugs: Structure-activity relationships. In: Iversen, L.L.; Iversen, S.D.; and Snyder, S.H., eds. *Handbook of Psychopharmacology*. Vol. 11. New York: Plenum, 1978. pp. 243-333.

Shulgin, A.T., and Carter, MF. Centrally active phenethylamines. *Psychopharmacology Communications* 1:93-98, 1975.

Young, R., and Glennon, R.A. Discriminative stimulus properties of amphetamine and structurally related phenalkylamines. *Med Res Rev* 6:99-130, 1986.

ACKNOWLEDGMENTS

Work supported in part by Public Health Service grant DA 01642 and by funding from the World Health Organization, the U.S. Drug Enforcement Administration, the VCU Grant-in-Aid Program, and the A.D. Williams Fund.

AUTHOR

Richard A. Glennon, Ph.D.
Department of Medicinal Chemistry
School of Pharmacy
Medical College of Virginia
Virginia Commonwealth University
Richmond, VA 23298-0581