Drug and Alcohol Dependence, 17 (1986) 119—134
Elsevier Scientific Publishers Ireland Ltd.

DISCRIMINATIVE STIMULUS PROPERTIES OF PHENYLISOPROPYLAMINE DERIVATIVES

RICHARD A. GLENNON

Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298 (U.S.A.)

SUMMARY

The phenylisopropylamine unit is a common structural fragment amongst many centrally-acting agents. However, these agents do not necessarily produce similar behavioral effects in test subjects. For example, the phenylisopropylamine derivative amphetamine is a central nervous system (CNS) stimulant whereas its 2,5-dimethoxy-4-methyl analog, i.e. DOM, is considered to be a hallucinogen. Employing animals trained to discriminate either (+)-amphetamine or (±)-DOM from saline in a two-lever operant procedure, stimulus generalization studies were conducted to evaluate members of a series of methoxy-substituted, and related, phenylisopropylamines. In this manner, it was possible to classify these agents as to which produced amphetamine-like effects, and which produced DOM-like effects.

Key words: Amphetamine — Stimulants — Hallucinogens — Cathinone — DOM — 3,4-methylene-dioxyamphetamine — 5-methoxy-3,4-methylene-dioxyamphetamine

INTRODUCTION

A number of agents are currently being considered by the World Health Organization (WHO) for possible international control (i.e. for scheduling) and most of these are derivatives of phenylisopropylamine. The phenylisopropylamine unit is common amongst many biologically-active agents, and the nature and location of pendant substituent groups is known to alter both activity and potency. For example, the unsubstituted parent phenylisopropylamine amphetamine (Fig. 1) is a central stimulant, whereas its 2,5-dimethoxy-4-methyl derivative, DOM, is a hallucinogenic agent. Shulgin [1] has suggested, and rightfully so, that substituted phenylisopropylamines not be referred to as substituted amphetamines. DOM is commonly called 2,5-

0376-8716/86/$03.50

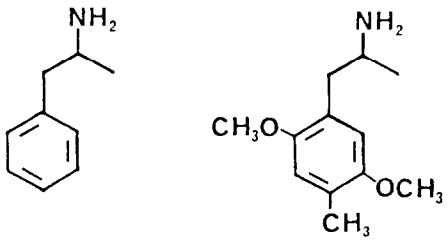


Fig. 1. Structures of the phenylisopropylamines (a) (±)-amphetamine (left and (b) (±)-DOM (right).

dimethoxy-4-methylamphetamine; amphetamine-type terminology is confusing and bears with it the connotation of 'amphetamine-like' activity. It is more acceptable to refer to these agents as substituted phenylisopropylamines, and it is even more appropriate to employ their chemical name; DOM, for instance, is 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane.

Various types of structural modification of the phenylisopropylamine unit are possible; some of these are shown in Fig. 2. The most common type of structural modification is methoxy substitution. Some other types of changes include methylenedioxy substitution, conversion of the benzylic methylene to a carbonyl group, to afford cathinone analogs, and, alteration of the terminal amine and/or α-methyl group (Fig. 2). What effect will each of these structural modifications have on amphetamine-like activity/potency?

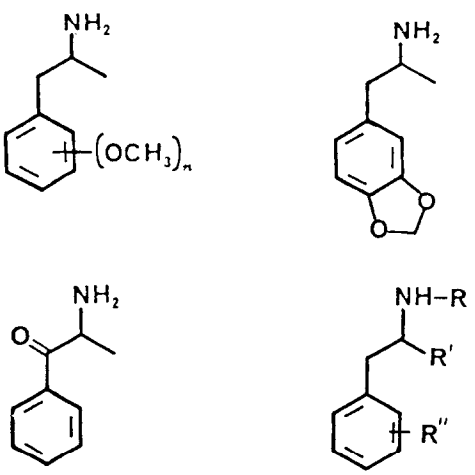


Fig. 2. Some structural modifications of the basic phenylisopropylamine moiety: (a) methoxy-substituted derivatives (upper left); (b) methylenedioxy derivatives (upper right); (c) benzylic carbonyl derivatives (lower left); and N-alkyl and α-alkyl derivatives (lower right).

Will any of these alterations convert the compound from one that produces amphetamine-like effects to one that might be more DOM-like? Some of these agents have been evaluated in human subjects employing appropriate clinical settings; but, this is the exception rather than the rule. For the most part, little human data (and, in some cases, even little to no animal data) are available for many of these structurally-modified phenylisopropylamines. One of the goals of our work was to examine a number of substituted and/or structurally-modified phenylisopropylamines in order to determine whether these agents might be classified as being amphetamine-like or DOM-like. The results of many of our studies have either been published or are currently in press. The present occasion affords the opportunity to summarize some of these results, particularly with respect to those agents being considered for scheduling. As a consequence, what follows should not be considered to be a comprehensive review of the literature, but is, rather, a review of some of our most recent findings.

GENERAL METHOD

The method that we selected to investigate these phenylisopropylamines was the discriminative stimulus or drug discrimination paradigm. Using a standard two-lever operant chamber, animals (rats) were trained to respond (i.e. to press either one of two levers) for a food (sweetened milk) reward under a variable interval 15-s (VI-15s) schedule of reinforcement. Once the animals achieved a consistent level of lever-pressing, they were then trained to press one lever when administered a training drug and to press the opposite lever when administered saline (1.0 ml/kg) using a 15-min pre-session injection interval. Two different training drugs were employed. One group of animals was trained to discriminate 1.0 mg/kg of racemic DOM hydrochloride (i.p.) from saline [e.g. 2], whereas the second group of animals was trained to discriminate 1.0 mg/kg of (+)-amphetamine sulfate (i.p.) from saline [e.g. 3]. Discriminative responding is a dose-related phenomenon; using DOM as an example, Fig. 3 shows that administration of 1.0 mg/kg of DOM to 1.0 mg/kg DOM-trained animals (n = 6 at each dose) results in greater than 90% DOM-appropriate responding. Administration of saline to these same animals results in less than 10% DOM-appropriate responding. Reduction of the dose of DOM administered to the 1.0 mg/kg DOM-trained animals results in a decrease in DOM-appropriate responding until a dose is reached at which the animals recognize this small dose as producing saline-like effects. From these results, DOM was found to possess an ED_{50}-value of 0.44 mg/kg in the 1.0 mg/kg DOM-trained animals [2]. Tests of stimulus generalization can now be conducted using the modified phenylisopropylamines. That is, the DOM-trained animals can be challenged with various doses of the modified phenylisopropylamine derivatives in order to determine whether or not the animals will recognize the challenge agents as producing stimulus effects similar to those produced by the training drug (i.e. 1.0 mg/kg of DOM). Agents that produce similar effects in humans often generalize

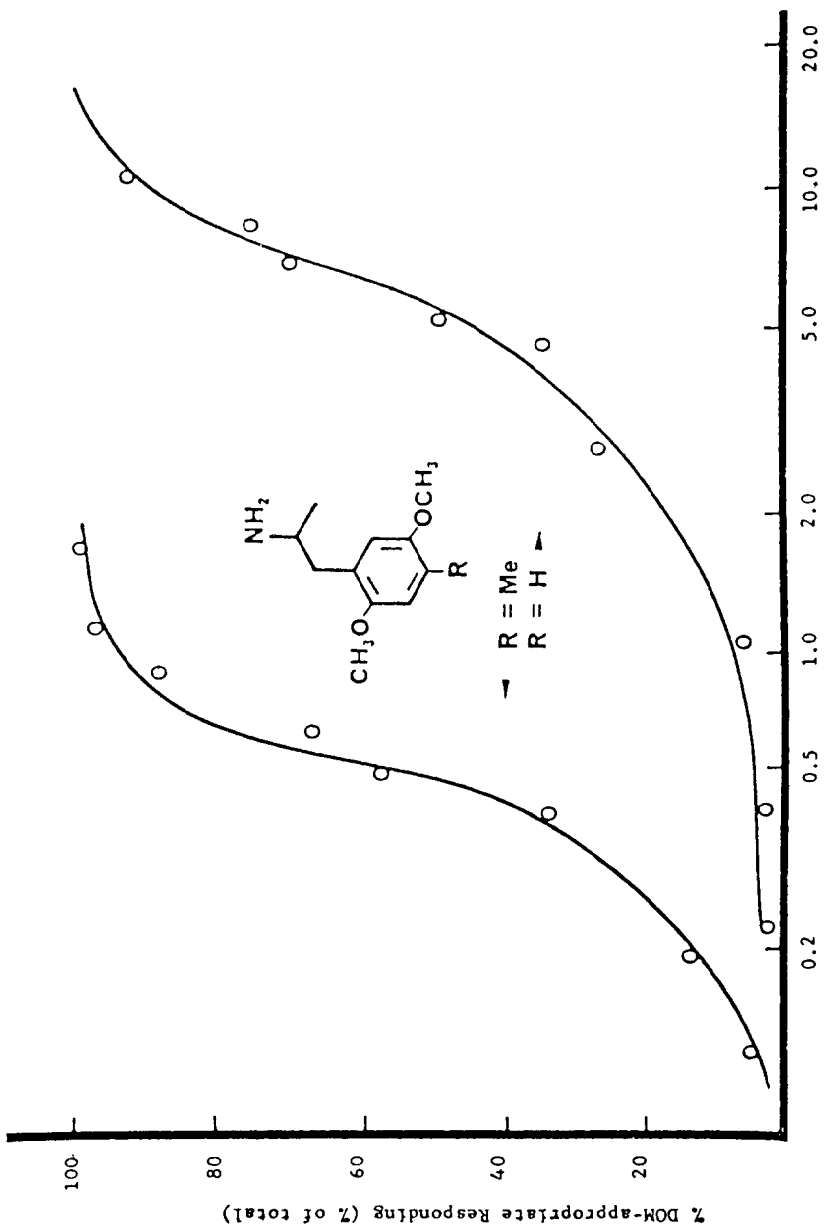


Fig. 3. Dose-response curves showing the effects of different doses of (±)-DOM (left) and (±)-2,5-DMA (right) in animals trained to discriminate 1.0 mg/kg of DOM from saline.

(substitute, transfer) to one another in tests of stimulus generalization in animals. Tests of stimulus generalization were conducted during 2.5-min extinction sessions. Thus, administration of various doses of, for example, the 4-demethyl derivative of DOM reveals that, at low doses, this agent produces saline-like effects, while at higher doses, this agent produces DOM-like effects (Fig. 3). The occurrence of stimulus generalization suggests that the two agents are capable of producing similar discriminative sitmulus effects. For those agents to which the DOM-stimulus generalizes, an ED_{50}-value can be calculated. Similar studies were conducted employing the (+)-amphetamine-trained animals. The results of these types of studies afforded data that are both qualitative and quantitative. Thus, it was possible to classify the modified phenylisopropylamines as being either DOM-like or amphetamine-like, and, it was further possible to quantitate these effects so that potency comparisons could be made between the challenge drugs and the respective training drug. Where stimulus generalization occurred, ED_{50}-values are presented in the tables that follow.

RESULTS

Cathinone related agents

S(—)-Cathinone is an active central stimulant component of fresh khat (*Catha edulis*); aged samples of khat contain a decreased level of cathinone, which may be the result of its conversion to (+)-cathine, i.e. (+)-norpseudoephedrine. Table I shows that cathinone does not produce DOM-appropriate responding but that it does produce amphetamine-like effects. In (+)-

TABLE I

EFFECT OF CATHINONE IN (±)-DOM-TRAINED AND (+)-AMPHETAMINE-TRAINED ANIMALS

	ED_{50} (mg/kg)	
	(±)-DOM (1.0 mg/kg)	(+)-AMPH (1.0 mg/kg)
Amphetamine:		
(±)-	Disrupt (2.0)[a]	0.62
S(+)-	—	0.42
R(—)	—	1.23
Cathinone:		
(±)-	—	0.72
S(—)-	Disrupt (1.5)[a]	0.34
R(+)-	—	4.41
Methamphetamine:		
S(+)-	Disrupt (1.5)[a]	0.40

[a]Number in parenthesis is lowest mg/kg dose at which disruption of behavior (i.e. no responding) was observed.

TABLE II

EFFECT OF CATHINONE AND RELATED AGENTS IN (±)-CATHINONE-TRAINED (0.6 mg/kg) ANIMALS

These studies were performed in collaboration with M. Schechter and J.A. Rosecrans [4—6].

	ED_{50} (mg/kg)
	(±)-Cathinone[a]
Amphetamine:	
S(+)-	0.21
Cathinone:	
(±)-	0.24
S(−)-	0.22
R(+)-	0.72
Cathine	1.61
(±)-Methamphetamine	0.17
Cocaine	1.97

[a] Cathinone hydrochloride (i.p.) was used as the training drug. Generalization studies employed hydrochloride salts except for amphetamine sulfate.

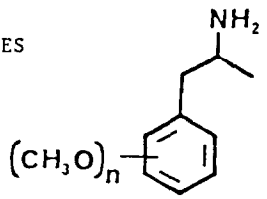
amphetamine-trained animals, the naturally-occurring S(−)-isomer of cathinone is approximately equiactive with S(+)-amphetamine but is twice as active as racemic cathinone and more than 10 times as active as its enantiomer R(+)-cathinone [3]. In a collaborative effort with Dr. M. Schechter of Northeastern Ohio Universities College of Medicine and Dr. J. Rosecrans of MCV/VCU to further study the stimulus properties of cathinone, rats were trained to discriminate 0.6 mg/kg of racemic cathinone hydrochloride from saline [4—6]. The results of some of our studies with these cathinone-trained animals are shown in Table II. Cathinone-stimulus generalization was observed both with amphetamine and methamphetamine. Whereas S(−)-cathinone was no more active than racemic cathinone, it was more active that R(+)-cathinone. (+)-Cathine also produced cathinone-like effects but was approximately one-eighth as active as S(−)-cathinone. As with amphetamine, (±)-cathinone-stimulus generalization occurred with cocaine and methamphetamine [6].

The results of these studies suggest that both cathinone and (+)-cathine are capable of producing amphetamine-like effects with S(−)-cathinone being approximately as active as S(+)-amphetamine and somewhat more active than (+)-cathine.

Methoxy-substituted phenylisopropylamines

Figure 4 reveals that there are 19 different positional isomers of methoxyphenylisopropylamine. In the course of our studies, we have investigated most of these positional isomers. Silverman and Ho [7] were the first to

METHOXY-SUBSTITUTED PHENYLISOPROPYLAMINES



	n	Number of positional isomers
Unsubstituted	0	1
Monomethoxy-	1	3
Dimethoxy-	2	6
Trimethoxy-	3	6
Tetramethoxy-	4	3
Pentamethoxy-	5	1

Fig. 4. Positional isomers of methoxy-substituted phenylisopropylamines.

TABLE III

EFFECT OF UNSUBSTITUTED AND MONO-METHOXY PHENYLISOPROPYLAMINES IN ANIMALS TRAINED TO DISCRIMINATE EITHER DOM OR (+)-AMPHETAMINE FROM SALINE

	ED_{50} (mg/kg)	
	(±)-DOM (1.0 mg/kg)	(+)-AMPH (1.0 mg/kg)
AMPH: (±)	Disrupt (2.0)	0.62
(+)	Disrupt (2.0)	0.42
(−)	Disrupt (2.0)	1.23
S(+)-N-Me AMPH[a]	—	0.40
(±)-OMA[b]	Disrupt (6.0)	7.82
(±)-MMA	Disrupt (5.0)	3.44
(±)-PMA[c]	Disrupt (1.5)	1.91

[a] S(+)-Methamphetamine.

[b] OMA, MMA and PMA are 2-methoxy-, 3-methoxy- and 4-methoxy-phenylisopropylamine, respectively.

[c] A 5-min pre-session injection interval was employed for the generalization studies in amphetamine-trained animals.

demonstrate that the DOM-stimulus does not generalize to amphetamine and that an amphetamine-stimulus does not generalize to DOM. The results shown in Tables III and V are consistent with these findings. Both isomers of amphetamine, along with racemic amphetamine, produce amphetamine-appropriate responding; S(+)-amphetamine is about three-times more potent than its R(−)-enantiomer [8]. Mono-methoxy substitution of phenylisopropylamine results in retention of amphetamine-like stimulus properties although each of the mono-methoxy derivatives is less potent than amphetamine itself (Table III). The general order of potency is: (±)-amphetamine > (±)-PMA > (±)-MMA > (±)-OMA (Glennon et al., unpublished results).

Of the six different positional isomers of dimethoxyphenylisopropylamine (DMA), none produced amphetamine-appropriate responding (Table IV). However, both 2,4-DMA and 2,5-DMA produced DOM-appropriate responding [9]. Nevertheless, these two agents were only about one-tenth as active as DOM itself. The R(−)-isomer of 2,5-DMA appears to be responsible for DOM-like activity in that it is about twice as active as its racemate; S(+)-2,5-DMA did not produce DOM-like effects. Both 2,4-DMA and 2,5-DMA have been demonstrated to be hallucinogenic in humans [1]; substitution at the 4-position of 2,5-DMA has also been shown to result in a number of agents that are psychoactive. As a result, a series of 4-substituted 2,5-DMA derivatives was studied in detail using DOM-trained animals.

DOM is the 4-methyl derivative of 2,5-DMA. As mentioned above, DOM is approximately ten times more active than 2,5-DMA. Both isomers of DOM produce DOM-appropriate responding with R(−)-DOM being about eight times more active than its S(+)-enantiomer (Table V). Homologation of this

TABLE IV

EFFECT OF DIMETHOXYPHENYLISOPROPYLAMINES IN ANIMALS TRAINED TO DISCRIMINATE EITHER DOM OR AMPHETAMINE FROM SALINE

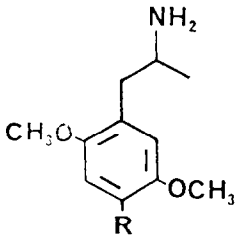
	ED_{50} (mg/kg)	
	(±)-DOM (1.0 mg/kg)	(+)-AMPH (1.0 mg/kg)
(±)-2,3-DMA	Disrupt (7.0)	Disrupt (6.5)
(±)-2,4-DMA	4.88	Disrupt (7.0)
(±)-2,5-DMA	5.51	Disrupt (13.9)
R(−)-	3.25	—[a]
S(+)-	Disrupt (15.0)	Saline (22% @ 9.0)[b]
(±)-2,6-DMA	Disrupt (13.8)	Saline (12% @ 15.0)[b]
(±)-3,4-DMA	Disrupt (12.0)	Disrupt (6.65)
(±)-3,5-DMA	Disrupt (15.0)	Saline (9% @ 7.0)[b]

[a] Not tested.

[b] Saline-appropriate responding at the highest dose tested; % AMPH-appropriate responding at highest dose tested given in parenthesis.

TABLE V

EFFECT OF 4-SUBSTITUTED HOMOLOGS OF DOM ON (±)-DOM-APPROPRIATE RESPONDING

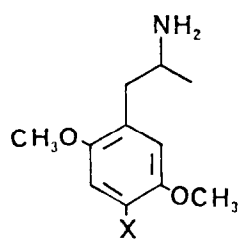


	R	ED_{50} (mg/kg)[a]
2,5-DMA	H	5.51
DOM	Me	0.44
R(−)-		0.21
S(+)-		1.70
DOET	Et	0.23
R(−)-		0.09
S(+)-		0.85
DOPR	*n*-Pr	0.17
DOBU	*n*-Bu	0.91
DOAM	*n*-Am	Disrupt (1.5)

[a]Animals trained to discriminate 1.0 mg/kg of DOM—HCl (i.p.) from saline.

TABLE VI

EFFECT OF 4-HALO ANALOGS OF DOM ON (±)-DOM-APPROPRIATE RESPONDING



	X	ED_{50} (mg/kg)[a]
2,5-DMA	H	5.51
DOF	F	1.45
DOB	Br	0.20
R(−)-		0.10
S(+)-		0.81
DOI	I	0.42
R(−)-		0.26
S(+)-		1.00

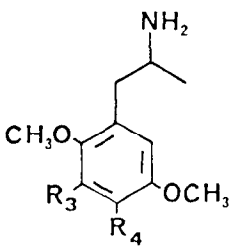
[a]Animals trained to discriminate 1.0 mg/kg of DOM—HCl (i.p.) from saline.

methyl group to an ethyl group affords DOET; DOET is slightly more potent than DOM, and again, the R(−)-isomer is about eight-times more potent than S(+)-DOET. Several additional homologs including the *n*-propyl (DOPR) and *n*-butyl (DOBU) derivatives produce DOM-appropriate responding [10]. 4-Halogenated derivatives of 2,5-DMA also result in active agents (Table VI). The only halogenated derivative currently being considered for scheduling is the 4-bromo analog of 2,5-DMA, i.e. DOB. DOB is considerably more active than 2,5-DMA in producing DOM-like effects [10]; this is easily seen if doses are compared in molar units and if it is realized that the molecular weight of DOB is considerably influenced by the bulky bromo group. Again, as with the alkyl derivatives, the R(−)-isomer of DOB is approximately eight-times more active than its S(+)-enantiomer.

The question was raised as to just how sensitive the DOM-trained animals are to the effects of only slight variations in structure. The enantiomeric comparisons presented in Tables V and VI offer one answer to this question. Another answer can be found in Table VII. Moving the aromatic methyl group of DOM from the 4-position to the 3-position results in a dramatic decrease in potency, and, in fact, in a compound that, at approx. 20-times the ED_{50} dose of DOM, produces only 34% DOM-appropriate responding. Likewise, moving the bromo group of racemic DOB from the 4-position to

TABLE VII

EFFECT OF 4- to 3-POSITION TRANSLOCATION ON (±)-DOM-APPROPRIATE RESPONDING



	R_3	R_4	ED_{50} (mg/kg)[a]
(±)-2,5-DMA:	H	H	5.51
(±)-DOM:	H	Me	0.44
	Me	H	(34% @ 8.0)[b]
(±)-2,4,5-TMA:	H	OCH_3	3.59
	OCH_3	H	7.90
(±)-DOB:	H	Br	0.20
	Br	H	(0% @ 3.0)[b]

[a] Animals trained to discriminate 1.0 mg/kg of DOM—HCl from saline. See text for discussion.

[b] Where stimulus generalization did not occur, % DOM-appropriate responding and dose that produced that response are given in parenthesis.

TABLE VIII

EFFECT OF TRIMETHOXYPHENYLISOPROPYLAMINES IN ANIMALS TRAINED TO DISCRIMINATE EITHER DOM OR AMPHETAMINE FROM SALINE

	ED_{50} (mg/kg)	
	(±)-DOM (1.0 mg/kg)	(+)-AMPH (1.0 mg/kg)
(±)-2,3,4-TMA	7.80	Disrupt (10.0)
(±)-2,3,5-TMA	16.48	Disrupt (10.0)
(±)-2,3,6-TMA	—[a]	—[a]
(±)-2,4,5-TMA	3.59	Disrupt (3.3)
(±)-2,4,6-TMA	3.69	Disrupt (8.5)
(±)-3,4,5-TMA	6.34	Disrupt (5.0)

[a]Not tested.

the 3-position results in an agent which, at more than 10-times the ED_{50} dose of DOB, produces 0% DOM-appropriate responding (Table VII). Thus, the animals appear to be very sensitive to the effects of minor structural modification.

Table VIII reveals that none of the trimethoxyphenylisopropylamines (TMA) produce amphetamine-appropriate responding (Glennon et al., unpublished results). However, all of the five TMA derivatives evaluated were shown to produce DOM-appropriate responding [9].

In summary, mono-methoxy substitution of phenylisopropylamine results in three positional isomers, OMA, MMA and PMA, that appear to produce amphetamine-like discriminative stimulus effects, but that are, nevertheless, somewhat less potent than the unsubstituted phenylisopropylamine amphetamine. Two of the di-methoxy derivatives, 2,4-DMA and 2,5-DMA, produce DOM-like effects whereas the remaining DMA analogs were found to produce neither DOM nor amphetamine-like effects under the conditions employed. Certain 4-alkyl derivatives (e.g. DOET) and 4-halo derivatives (e.g. DOB) of 2,5-DMA produced DOM-like effects. These agents were more potent than either 2,5-DMA or DOM (on a molar basis) and, in general, their R(−)-isomers were more potent than their racemates and/or S(+)-enantiomers. None of the TMA derivatives produced amphetamine-like effects, whereas they all produced DOM-like effects.

N-Methyl and α-demethyl phenylisopropylamines

Extensive studies have not been conducted with these types of agents. Nevertheless, the results of our initial work provide evidence for the existence of certain trends.

N-Monomethylation of agents that produce amphetamine-like effects seems to have little effect either on activity or potency. In fact, N-methyl-

ation may even slightly enhance the amphetamine-like discriminative potency of an agent. For example, N-monomethylation of S(+)-amphetamine to afford S(+)-*N*-methylphenylisopropylamine, or S(+)-methamphetamine to no effect on potency (Table III) [8]. The effect of di-methylation has not yet been investigated. In contrast, N-monomethylation of agents that produce DOM-like effects results in a decreased potency [11]. For example, N-methyl DOM (N-Me DOM) is several-fold less potent than DOM [11]. *N*,N-Dimethylation results in an even further decrease in potency.

Removal of the α-methyl group of amphetamine affords phenethylamine; at a dose more than 10-times greater than the ED_{50} dose of S(+)-amphetamine, phenethylamine produced saline-like (i.e. 6% amphetamine-appropriate) responding [3]. Similar results were obtained, for example, with the α-demethyl derivative of cathinone [3]. In general, removal of the α-methyl group of agents that produce DOM-appropriate responding results in a decrease in potency. For example, α-demethyl DOM is two- to three-times less potent than DOM itself [11]. Likewise, α-demethylation of 3,4,5-TMA, to afford mescaline, results in slightly more than a 2-fold decrease in potency [9].

Methylenedioxy derivatives

There are two positional isomers of methylenedioxyphenylisopropylamine or MDA (more commonly, but less accurately, referred to as methylenedioxyamphetamine). These are 2,3-MDA and 3,4-MDA. 2,3-MDA was recently synthesized by Soine et al. [12] at MCV/VCU. Table IX demonstrates that neither the DOM-stimulus nor the amphetamine-stimulus gener-

TABLE IX

EFFECT OF METHYLENEDIOXYPHENYLISOPROPYLAMINES IN ANIMALS TRAINED TO DISCRIMINATE EITHER 1.0 mg/kg OF DOM OR 1.0 mg/kg OF (+)-AMPHETAMINE FROM SALINE

	ED_{50} (mg/kg)	
	(±)-DOM (1.0 mg/kg)	(+)-AMPH (1.0 mg/kg)
(±)-2,3-MDA	Disrupt (6.0)	Disrupt (3.0)
(±)-MMDA-2[b]	3.36	—[a]
(±)-3,4-MDA	1.68	2.29
R(−)-	0.81	Disrupt (2.25)
S(+)-	Disrupt (2.0)	0.90
(±)-MDMA[c]	Disrupt (2.5)	1.64
R(−)-	Disrupt (2.5)	—
S(+)-	Disrupt (2.0)	—

[a] Not tested.
[b] 1-(2-Methoxy-4,5-methylenedioxyphenyl)-2-aminopropane.
[c] N-Methyl-3, 4-MDA, 'Ecstasy'.

TABLE X

STIMULUS CHARACTERISTICS OF DOM, 3,4-MDA (MDA) AND AMPHETAMINE (AMPH)

Generalization to:	Stimulus[a]		
	DOM	MDA	AMPH
(a) (±)-DOM	Yes	Yes	No
(b) R(−)-DOM	Yes	—	No
(c) S(+)-DOM	Yes	—	No
(d) (±)-MDA	Yes	Yes	Yes
(e) R(−)-MDA	Yes	Yes	No
(f) S(+)-MDA	No	Yes	Yes
(g) (+)-AMPH	No	Yes	Yes
(h) LSD	Yes	Yes	No
(i) Cocaine	No	Yes	Yes
(j) 2.3-MDA	No	Yes	No
(k) 3,4-DMA	No	Yes	No

[a] Animals were trained to discriminate either 1.0 mg/kg of racemic DOM—HCl, 1.5 mg/kg of racemic 3,4-MDA—HCl, or 1.0 mg/kg of (+)-amphetamine sulfate from saline.

alizes to 2,3-MDA [13]. 3,4-MDA (previously referred to simply as MDA) has been reported to be a drug of abuse (the 'Love Drug'). Interestingly, 3,4-MDA is the only agent that we have studied to date that appears to produce both amphetamine-like and DOM-like discriminative stimulus effects [14]. A close examination of the optical isomers of 3,4-MDA reveals that R(−)-3,4-MDA, but not S(+)-3,4-MDA, produces DOM-appropriate responding, while the opposite is true for amphetamine-appropriate responding [8]. Furthermore, consistent with our previous findings regarding the potencies of optical isomers, R(−)-3,4-MDA is more potent than its racemate in producing DOM-like effects, whereas S(+)-3,4-MDA is more potent than its racemate in producing amphetamine-like effects (Table IX).

We were so intrigued by the interesting results obtained with 3,4-MDA that we trained a small group of animals to discriminate 1.5 mg/kg of (±)-3,4-MDA hydrochloride from saline [14]. Results of generalization studies employing these 3,4-MDA-trained animals reveal that these animals recognized the effects produced both by amphetamine and by DOM (Table X). In addition, whereas DOM-trained, but not amphetamine-trained, animals recognize LSD, and while amphetamine-trained, but not DOM-trained, animals recognize cocaine, (±)-3,4-MDA-stimulus generalization occurs both to LSD and cocaine [15] (Table X). On the other hand, agents such as 3,4-DMA and 2,3-MDA, which produced neither DOM-like nor amphetamine-like effects also result in 3,4-MDA-stimulus generalization when administered to the MDA-trained animals [13,15].

Another agent being considered for scheduling is the N-methyl analog of (±)-3,4-MDA, or *N*-methyl-3,4-methylenedioxyphenylisopropylamine (i.e.

methylenedioxymethamphetamine; MDMA, 'Ecstasy'). We had earlier described the general effect of N-methylation; that is, N-methylation of agents that produce DOM-like effects results in a reduction of potency; whereas N-methylation of agents that produce amphetamine-like activity does not appear to produce an untoward effect (i.e. produces a slight increase, or has no effect, on potency). The results obtained with MDMA appear to follow this trend. Neither (±)-MDMA nor either of its optical isomers produce DOM-appropriate responding [16]. However, (±)-MDMA does produce amphetamine-appropriate responding, and, as such, it is slightly more potent than (±)-3,4-MDA (Table IX). Apparently, N-monomethylation of 3,4-MDA converts the compound from one that produces both amphetamine-like and DOM-like stimulus effects of one that possesses predominantly amphetamine-like discriminative stimulus properties. In other words, N-monomethylation of 3,4-MDA appears to reduce (or abolish) its DOM-like effects, while at the same time, it unmasks (and even somewhat enhances) its amphetamine-like stimulus properties.

CONCLUSION

Using the drug discrimination paradigm with animals trained to discriminate either 1.0 mg/kg of racemic DOM from saline, or 1.0 mg/kg of (+)-amphetamine from saline, it was possible to classify various phenylisopropylamine derivatives as being able to produce effects that were: (a)

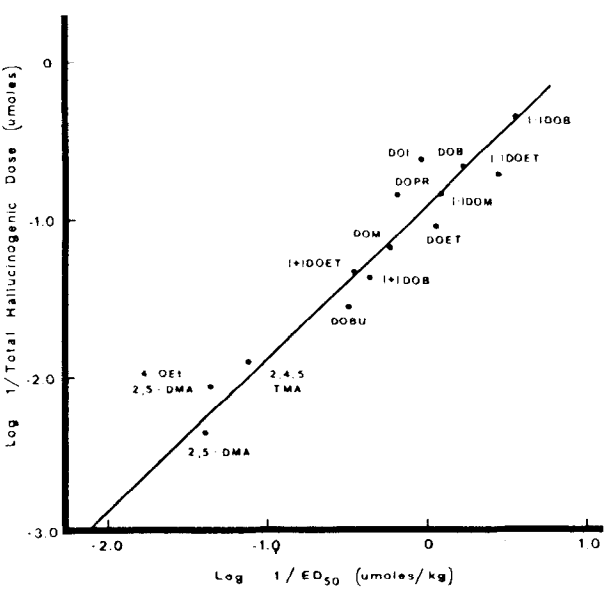


Fig. 5. Relationship between discrimination-derived ED_{50}-values (from 1.0 mg/kg DOM-trained animals) and human hallucinogenic potencies [10].

similar to those produced by DOM, (b) similar to those produced by (+)-amphetamine, (c) similar to those produced by both DOM and (+)-amphetamine, or (d) dissimilar to those produced by either DOM or (+)-amphetamine. ED_{50}-values were calculated, for those agents that produced DOM-like or amphetamine-like effects, providing potency comparisons. Approximately 20 of the agents (or optical isomers) evaluated herein have been previously reported to produce hallucinogenic effects in humans. As a test of the validity of this method for accumulating information which might prove relevant to the human situation, we sought to determine if a relationship might exist between these human hallucinogenic potencies and discrimination-derived ED_{50}-values (in DOM-trained animals). The results, previously published in the Journal of Medicinal Chemistry [10], are reproduced as Fig. 5. It is certainly recognized that there are a variety of limiting factors and inherent problems associated with quantitation of hallucinogenic potencies in human subjects. Nevertheless, the results suggest that, indeed, a relationship may exist between human potency and discrimination-derived data as shown in Fig. 5.

Hopefully, the studies presented herein [2—6, 8—11, 13—16 and unpublished data] will be of some value in classifying the discriminative stimulus properties of structurally modified phenylisopropylamine derivatives, and might aid in the deliberations regarding the possible scheduling of certain of these agents.

DISCUSSION OF TALK BY DR. GLENNON

Roland Griffiths (Division of Behavioral Biology, Johns Hopkins University School of Medicine, Baltimore, MD, U.S.A.): That's a very impressive set of data you've put together. One point I may have missed, about the MDA-trained animals: was that the racemate?

Glennon: That is right. We used racemic MDA. In that connection, there is one study we would very much like to do: we are using two groups of animals. One group is trained up to amphetamine. The second group is trained up to DOM. Perhaps we could achieve the same results by training up animals to discriminate one isomer of MDA from the other isomer of MDA and, rather than having two separate groups of animals, put the compounds into the MDA-trained animals, and see if they are more minus- or plus-like. It is something we would like to do eventually. I might add that, of all the compounds that we have studied, one of the most difficult drugs to train the animals to was MDA. It took nearly a year to train up these MDA animals, and it is probably because the animals were trying to recognize both components of the cue.

James Woods (Department of Pharmacology, University of Michigan Medical School, Ann Arbor, MI, U.S.A.): I might mention that we've asked Dr. Glennon to work with us on the compounds that are under consideration. We hope to be able to work out an arrangement whereby he can examine with his procedures those compounds that haven't been assessed.

ACKNOWLEDGEMENTS

The work described in this presentation was supported, in part, by PHS Grant DA-01642, and by the WHO, Division of Mental Health. I would also

like to take this opportunity to acknowledge the considerable contribution to this research by Dr. R. Young.

REFERENCES

1 A.T. Shulgin, in: L.L. Iversen, S.D. Iversen and S.H. Snyder (Eds.), Handbook of Psychopharmacology, 243; Plenum Press, New York, 1978.
2 R. Young, R.A. Glennon and J.A. Rosecrans, Comm. Psychopharmacol., 4 (1981) 501.
3 R.A. Glennon et al., Pharmacol. Biochem. Behav., 21 (1984) 895.
4 M.D. Schechter, J.A. Rosecrans and R.A. Glennon, Pharmacol. Biochem. Behav., 20 (1984) 181.
5 R.A. Glennon, M.D. Schechter and J.A. Rosecrans, Pharmacol. Biochem. Behav., 21 (1984) 1.
6 M.D. Schechter and R.A. Glennon, Pharmacol. Biochem. Behav., 22 (1985) 913.
7 P.B. Silverman and B.T. Ho, Psychopharmacology, 68 (1980) 209.
8 R.A. Glennon and R. Young, Pharmacol. Biochem. Behav., 20 (1984) 501.
9 R.A. Glennon and R. Young, Pharmacol. Biochem. Behav., 17 (1982) 603.
10 R.A. Glennon et al., J. Med. Chem., 25 (1982) 1163.
11 R.A. Glennon, R. Young and J.M. Jacyno, Biochem. Pharmacol., 32 (1983) 1267.
12 W.H. Soine, R.E. Shark and D.T. Agee, J. Forensic Sci., 28 (1983) 386.
13 R.A. Glennon, R. Young and W. Soine, Gen. Pharmacol., 15 (1984) 361.
14 R.A. Glennon and R. Young, Life Sci., 34 (1984) 379.
15 R.A. Glennon and R. Young, Eur. J. Pharmacol., 99 (1984) 249.
16 R.A. Glennon et al., Biol. Psychiatry, 17 (1982) 807.