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Comparison of Behavioral Properties of Di- and Tri-methoxyphenylisopropylamines

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GLENNON, R. A. AND R. YOUNG. *Comparison of behavioral properties of di- and tri-methoxyphenylisopropylamines.* PHARMAC. BIOCHEM. BEHAV. 17(4) 603–607, 1982.—Prominent among the class of hallucinogenic phenylisopropylamines is the 2,5-dimethoxy substitution pattern; this pattern has long been recognized as being an important feature of the more potent agents within this class. The purpose of this present study was to explore the behavioral properties of a series of methoxylated phenylisopropylamines in order to determine the effect of other substitution patterns and the relative importance of individual methoxy groups. Rats, trained to discriminate the hallucinogenic agent 2,5-dimethoxy-4-methyl-phenylisopropylamine (DOM) from saline in a two-lever drug discrimination task, were challenged with a series of di- and trimethoxyphenylisopropylamines (i.e., DMA and TMA derivatives). DOM-stimulus generalization was found to occur with 2,4-DMA but not with 2,3-DMA, 2,6-DMA, or 3,5-DMA; generalization also occurred with 2,3,4-TMA, 2,3,5-TMA, 2,4,6-TMA and 3,4,5-TMA. The 2,4-dimethoxy pattern also emerges as an important feature among the more active agents.

Methoxyphenylisopropylamines Hallucinogenic phenylisopropylamines Hallucinogenic amphetamines
Structure-activity relationships Discriminative stimulus properties DOM

THERE exist six possible positional isomers of dimethoxyphenylisopropylamine (dimethoxyamphetamine, DMA). Of these, the hallucinogenic agent 2,5-DMA is the most prominent, and a special significance has been attached to the 2,5-dimethoxy substitution pattern which also occurs in a number of other potent psychoactive agents such as 2,5-dimethoxy-4-methylphenylisopropylamine (DOM) and 2,5-dimethoxy-4-bromophenylisopropylamine (DOB). Of the remaining dimethoxy isomers, one (2,4-DMA) is reported to be hallucinogenic, three (2,3-DMA, 2,6-DMA and 3,5-DMA) have not been evaluated in human studies, and one (3,4-DMA) is essentially inactive as a hallucinogenic agent (see [13] for a detailed discussion of the human pharmacology of 2,4-DMA, 2,5-DMA and 3,4-DMA). For the most part, with the exception of 2,5-DMA, the dimethoxy isomers have not been the object of extensive study.

We have previously used the discriminative stimulus paradigm to investigate the behavioral (stimulus) properties of various phenylisopropylamines, particularly those derivatives bearing the 2,5-dimethoxy substitution pattern [6, 7, 9]. For example, employing rats trained to discriminate the hallucinogen 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT) from saline, stimulus generalization was found to occur with 2,5-DMA, but not with 3,4-DMA [6]. Furthermore, analogous to the human situation, 2,5-DMA was found to be one-tenth as active as DOM in discrimination studies employing DOM as the training drug [7], while DOM-stimulus generalization did not occur with 3,4-DMA [8]. Due to the lack of knowledge concerning the stimulus properties of the entire series of DMA derivatives, the object of the present study was to investigate the effects of these agents in animals trained to discriminate DOM from saline in order (a) to compare their stimulus properties with those of DOM (i.e., to determine which agents are capable of producing a DOM-like response in rats) and (b) to determine the relative importance and/or contribution of the various methoxy substituents to activity. Furthermore, because 2,4-DMA has been demonstrated to be hallucinogenic in man [13], particular emphasis was placed on evaluating additional derivatives of this agent, including several trimethoxyphenylisopropylamines (trimethoxyamphetamines, TMA) which either possess or lack the 2,4-dimethoxy substitution pattern.

METHOD

The drug discrimination training procedure for these animals has been reported previously [16]. Specifically, twenty-four male Sprague-Dawley rats were trained to discriminate racemic DOM (1.0 mg/kg) from saline in a two-lever operant task. In this procedure the administration of saline or DOM, 15 minutes prior to a variable interval 15-second (VI-15 sec) schedule of reinforcement served as the discriminative cue for the correct (reinforced) lever. Occasional periods (2.5 min) of non-reinforced lever responding were used to assess the degree of stimulus control exerted by saline and DOM over behavior, and, to evaluate various di- and tri-methoxy phenylisopropylamines. For those compounds where generalization (transfer) occurred, ED_{50} values were determined from the dose-response data by the method of Litchfield and Wilcoxin [11].

Drugs

All drugs used in this study were previously synthesized

TABLE 1

RESULTS OF GENERALIZATION STUDIES

Agent	Dose (mg/kg)	N*	% DOM-Appropriate Responding (±SEM)	Mean Responses/ Minute (±SEM)	ED_{50} (mg/kg)†	Human Hallucinogenic Dose (mg)‡
2,3-DMA	1.0	5/5	0%	14.5 (2.1)	—	—
	2.0	5/5	2% (1.8)	12.2 (1.0)		
	4.0	4/5	5% (4.1)	5.5 (1.3)		
	6.0	2/6	—	—		
	8.0	1/5	—	—		
2,4-DMA	3.0	5/5	7% (4.3)	12.6 (1.5)	4.88 (3.66–6.49)	60
	4.5	3/3	32% (14.6)	11.5 (1.9)		
	6.0	4/5	78% (15.1)	9.8 (1.4)		
	7.0	4/5	89% (7.8)	14.8 (2.1)		
2,5-DMA¶					5.80	50
2,6-DMA	5.0	5/5	11% (6.5)	10.8 (3.3)	—	—
	10.0	5/5	41% (6.9)	12.5 (2.5)		
	12.5	4/5	42% (16.4)	9.5 (2.6)		
	13.0	3/5	41% (10.1)	8.9 (1.6)		
	13.25	2/5	—§	—		
	15.0	2/5	—§	—		
3,4-DMA¶			—§		—	—
3,5-DMA	5.0	5/5	4% (3.6)	10.1 (2.6)	—	—
	10.0	5/5	6% (2.3)	13.2 (1.8)		
	12.5	3/5	14% (5.4)	10.5 (1.8)		
	15.0	2/5	—§	—		
2,3,4-TMA	5.0	5/5	29% (11.1)	12.3 (1.1)	7.80 (5.15–11.81)	—
	10.0	5/5	46% (21.6)	11.0 (2.6)		
	12.5	5/5	76% (10.7)	10.2 (1.8)		
	15.0	5/5	95% (3.3)	12.4 (1.5)		
2,3,5-TMA	5.0	5/5	8% (4.5)	14.4 (2.3)	16.48 (10.21–26.58)	—
	10.0	5/5	13% (8.1)	10.8 (1.1)		
	15.0	5/6	30% (12.9)	10.0 (2.1)		
	20.0	3/5	62% (22.1)	11.0 (1.7)		
	22.5	3/5	82% (12.4)	12.0 (1.9)		
2,4,5-TMA¶					3.59	20
2,4,6-TMA	1.0	5/5	4% (2.1)	12.4 (1.8)	3.69 (2.14– 6.36)	30–40
	3.0	5/5	38% (21.7)	11.5 (1.2)		
	5.0	5/5	62% (14.2)	11.4 (2.1)		
	7.0	4/5	84% (3.5)	10.3 (2.3)		
3,4,5-TMA	2.0	5/5	8% (3.8)	13.2 (1.7)	6.34 (4.22– 9.51	160–220
	3.0	5/5	29% (19.7)	10.4 (1.9)		
	4.0	5/5	41% (12.3)	10.4 (2.7)		
	8.0	5/5	68% (13.7)	11.8 (1.2)		
	10.0	5/5	77% (10.5)	11.2 (1.5)		
	11.0	5/5	79% (9.3)	12.1 (1.0)		
	13.0	5/5	84% (10.5)	9.8 (2.1)		
5-Me 2,4-DMA	2.5	3/3	28% (10.9)	11.3 (2.8)	3.18 (2.26– 4.48)	—
	3.5	2/4	49% (11.0)	9.0 (1.0)		
	4.25	3/3	85% (7.9)	11.7 (1.5)		
5-Br 2,4-DMA	3.0	5/5	4% (1.8)	13.2 (2.3)	6.69 (5.67– 7.89)	100
	4.5	5/5	6% (3.3)	10.0 (2.1)		
	5.5	5/5	23% (15.1)	11.6 (3.2)		
	7.0	5/5	51% (19.0)	10.1 (1.8)		
	7.5	4/5	68% (20.6)	12.3 (2.6)		
	8.0	3/5	80% (11.9)	13.0 (1.1)		
	9.0	2/5	—§	—		

TABLE 1

RESULTS OF GENERALIZATION STUDIES
(Continued)

Agent	Dose (mg/kg)	N*	% DOM-Appropriate Responding (±SEM)	Mean Responses/ Minute (±SEM)	Human ED_{50} (mg/kg)†	Hallucinogenic Dose (mg)‡
5-OEt 2,4-DMA	3.0	5/5	12% (6.3)	14.8 (1.3)	10.15 (4.97–20.72)	—
	6.0	5/5	28% (9.7)	13.8 (2.4)		
	12.0	4/5	56% (22.4)	10.5 (2.3)		
	18.0	3/5	63% (5.8)	9.4 (1.9)		
	19.0	3/5	82% (5.6)	8.9 (2.2)		
	20.0	1/5	—§	—		
6-Me 2,4-DMA	2.5	5/5	27% (8.8)	13.7 (2.0)	3.46 (2.62– 4.56)	—
	3.5	5/5	43% (13.3)	13.8 (1.1)		
	4.25	5/5	65% (21.6)	10.3 (1.9)		
	5.0	4/5	85% (7.7)	10.7 (1.8)		
Mescaline	10.0	5/5	23% (12.0)	10.7 (2.7)	14.64 (10.90–19.68)	300–350
	15.0	5/5	41% (9.6)	11.3 (1.6)		
	20.0	4/5	71% (5.6)	10.5 (2.0)		
	25.0	4/5	96% (2.3)	11.2 (1.8)		
DOM¶	1.0	24/24	98% (1.2)	15.0 (2.5)	0.44¶	2–5
Saline (1 ml/kg)		24/24	5% (2.2)	14.9 (3.1)		

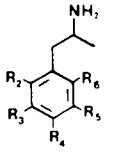
*Number of animals responding of number of animals tested at a particular dose.
†With 95% confidence limits.
‡Total (mg) human hallucinogenic dose [13].
§Disruption of behavior (i.e., no responding).
¶Data previously reported [7,8]; included for comparative purposes.

in our laboratory and were on hand as a result of earlier studies; the structures of these agents are shown in Fig. 1. Hydrochloride salts were employed throughout. Solutions were prepared fresh daily in sterile saline; drugs were administered via intraperitoneal injection.

RESULTS AND DISCUSSION

With respect to the simple dimethoxy derivatives, DOM-stimulus generalization occurs with 2,5-DMA [7] and 2,4-DMA; neither 3,4-DMA [8], 2,3-DMA, 2,6-DMA nor 3,5-DMA completely substitutes for DOM (Table 1). Where stimulus generalization occurred, it did so in a dose-related manner; response rates were not significantly different under drug or saline conditions except where complete disruption of behavior was observed (Table 1).

Additional substitution of the 2,4-DMA molecule by a 5-ethoxy (5-OEt 2,4-DMA) 5-bromo (5-Br 2,4-DMA), 5-methyl (5-Me 2,4-DMA) or 6-methyl (6-Me 2,4-DMA) group resulted in active compounds. The DOM-stimulus generalized with all four of these compounds, however, only the 5-methyl and 6-methyl derivatives of 2,4-DMA were more potent than its parent (Table 1). DOM stimulus generalization also occurred to all five trimethoxyphenylisopropylamines; Two of the TMA derivatives that possess the 2,4-dimethoxy groups (i.e., 2,4,5-TMA [9] and 2,4,6-TMA) were found to be more potent than 2,4-DMA; 2,3,4-TMA and the two derivatives which lack the 2,4-dimethoxy pattern were less active. Cross-generalization has been demonstrated between DOM and mescaline when either DOM [14] or mescaline [15] has been used as the training drug. Mes-



	R_2	R_3	R_4	R_5	R_6
2,3 -DMA	OCH_3	OCH_3	H	H	H
2,4 -DMA	OCH_3	H	OCH_3	H	H
2,5 -DMA	OCH_3	H	H	OCH_3	H
2,6 -DMA	OCH_3	H	H	H	OCH_3
3,4 -DMA	H	H	OCH_3	OCH_3	H
3,5 -DMA	H	OCH_3	H	OCH_3	H
2,3,4-TMA	OCH_3	OCH_3	OCH_3	H	H
2,3,5-TMA	OCH_3	OCH_3	H	OCH_3	H
2,4,5-TMA	OCH_3	H	OCH_3	OCH_3	H
2,4,6-TMA	OCH_3	H	OCH_3	H	OCH_3
3,4,5-TMA	H	OCH_3	OCH_3	OCH_3	H
5-Me 2,4-DMA	OCH_3	H	OCH_3	CH_3	H
5-Br 2,4-DMA	OCH_3	H	OCH_3	Br	H
5-OEt2,4-DMA	OCH_3	H	OCH_3	OC_2H_5	H
6-Me 2,4-DMA	OCH_3	H	OCH_3	H	CH_3
DOM	OCH_3	H	CH_3	OCH_3	H

FIG. 1. Structures and abbreviations of agents used in this study.

caline was included in the present study for comparative purposes (Table 1); our results are consistent with those reported by Silverman and Ho [14].

Interestingly, only those two DMA derivatives that have been shown to be hallucinogenic in man substituted for DOM (i.e., 2,5-DMA and 2,4-DMA); the other four isomers of DMA do not appear to produce DOM-like effects. Addition of a third methoxy group to the 2,4-DMA structure can either increase or decrease activity depending upon the location of this substituent. For example, the 5-methoxy and 6-methoxy derivatives (2,4,5-TMA and 2,4,6-TMA, respectively) were essentially equiactive, both being somewhat more active than 2,4-DMA itself. Incorporation of the third methoxy group between the two existing methoxy groups of 2,4-DMA (i.e., 2,3,4-TMA) halves activity. This finding is not surprising in light of recent suggestions that several adjacent methoxy groups will interfere with the preferred spatial orientation of one or more of the individual groups [2, 4, 5]. The two TMA derivatives lacking the 2,4-dimethoxy pattern (i.e., 2,3,5-TMA and 3,4,5-TMA) are less active than either 2,4,5-TMA or 2,4,6-TMA; 2,3,5-TMA is actually less active than the phenethylamine derivative mescaline.

Substitution of 2,4-DMA at the 5-position with either an ethoxy group (5-OEt 2,4-DMA) or a bromo group (5-Br 2,4-DMA) reduced, but does not abolish, activity (i.e., ability to produce DOM-like effects). On the other hand, 6-methylation, to afford 6-Me 2,4-DMA, enhances activity. In an earlier study [6], using animals trained to discriminate 5-OMe DMT from saline, 6-Me 2,4-DMA was demonstrated to be slightly more active than 2,4,6-TMA; the results of the present study support our earlier findings.

In general, there is good agreement between the data reported herein and the human activity of these agents. In fact, for those agents in Table 1 where DOM-stimulus generalization occurred there is a significant correlation ($r=0.947$, $n=8$) between ED_{50} (log $1/ED_{50}$) and total human hallucinogenic dose (log 1/total mg dose). Certain compounds were necessarily excluded from this comparison due to the lack of available human data. For example, 2,3-DMA, 2,6-DMA, 3,5-DMA and 6-Me 2,4-DMA have not been evaluated in man; 2,3,5-TMA and 5-OEt 2,4-DMA, agents that were only weakly active in the discrimination paradigm, are inactive in man [13], but have only been tested at relatively low doses, i.e., up to total doses of 50 mg and 30 mg, respectively. Likewise, 2,3,4-TMA is inactive in man at total doses of up to 100 mg [13]. The latter three agents may, indeed, have shown some activity in man had higher doses been evaluated.

What is the role, or relative contribution to activity, of the various aromatic substituents? The role of substituents at the 4-position of phenylisopropylamines has not yet been satisfactorily explained although such substituents might interfere with the metabolism of the aromatic nucleus [13] and/or might directly contribute to a receptor interaction [12]. By themselves, they do not appear to confer hallucinogenic properties to the phenylisopropylamine molecule. For example, 4-methylphenylisopropylamine is not hallucinogenic in man [13]; 4-methoxyphenylisopropylamine, although psychoactive in man [13], may produce effects which are dissimilar to those produced by DOM. In several animal species, 4-methoxyphenylisopropylamine produced gross behavioral effects more common to amphetamine than to DOM, 2,5-DMA, DOB or mescaline [3]. When administered to rats trained to discriminate DOM from saline, neither the 4-methyl nor the 4-methoxy derivative resulted in DOM-stimulus generalization [9,14]. Addition of a second methoxy group produces varying effects. Comparing the activity of 2,4-DMA with that of 3,4-DMA (=4,5-DMA), it appears that the 2-methoxy group contributes more, than does the 5-methoxy group, to producing a DOM-like response. This is in agreement with an earlier suggestion by Aldous *et al.* [1], although Ho *et al.* [10] have reported that the presence of a 2-methoxy group in such compounds is probably not responsible for producing disruptive behavior in animals. The importance of the 2-methoxy group is also apparent when the activity of 2,4,5-TMA is compared with 3,4,5-TMA. Because 2,4,5-TMA is more active than 2,4-DMA, the 5-methoxy group evidently contributes to activity. However, moving this methoxy group from the 5- to the 6- position (i.e., comparing 2,4,5-TMA with 2,4,6-TMA) has little effect on behavioral activity (Table 1) or human hallucinogenic activity [13]. Replacement of the 4-methoxy group of 2,4,5-TMA or 2,4,6-TMA with a methyl group enhances human hallucinogenic potency [13], as well as potency in tests of discriminative control of responding [6], in both cases. It is concluded that the single most important methoxy group is that at the 2-position while the presence of a substituent at the 4-position contributes to activity (perhaps for the reasons mentioned above). Additional substitution by methoxy groups at the 5- and 6-positions serve to further enhance activity. It should be emphasized, however, that these structure-activity relationships (SAR) are derived from in vivo studies and, as such, may not necessarily reflect the SAR for direct receptor-mediated phenomena. Nevertheless, the results of this present study suggest that the 2,4-disubstitution pattern of hallucinogenic phenylisopropylamines deserves more attention that it has been previously accorded.

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