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Discriminative Stimulus Properties of DOM and Several Molecular Modifications

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GLENNON, R. A., R. YOUNG AND J. A. ROSECRANS. *Discriminative stimulus properties of DOM and several molecular modifications.* PHARMAC. BIOCHEM. BEHAV. **16**(4) 553–556, 1982.—Rats trained to discriminate racemic 2,5-dimethoxy-4-methylphenylisopropylamine, (±)-DOM (1.0 mg/kg), from saline in a two-lever drug discrimination task were challenged with the optical isomers of DOM as well as with several related agents which represent minor molecular modifications of the DOM structure. Generalization of the (±)-DOM stimulus was found to occur to R(−)-DOM, S(+)-DOM, (±)-2,5-dimethoxyphenylisopropylamine (2,5-DMA), R(−)-2,-5-DMA, and the 2-demethyl derivative of (±)-DOM. The 3-methyl positional isomer of (±)-DOM was found to produce only 34% DOM-appropriate responding at the highest dose tested while administration of S(+)-2,5-DMA and the 5-demethyl derivative of (±)-DOM resulted in disruption of behavior.

DOM Discriminative stimulus properties DOM molecular modifications
2,5-Dimethoxy-4-methylphenylisopropylamine Hallucinogens

2,5-DIMETHOXY-4-methylphenylisopropylamine (DOM, "STP") has been shown to be a potent psychotomimetic agent in man [7,8]. R(−)-DOM, the more active isomer of DOM, is reported as being more than four times as active as its S(+)-enantiomer [5], while (±)-DOM is approximately ten times more active than racemic 2,5-dimethoxyphenylisopropylamine (2,5-DMA) in human studies [1]. In an attempt to determine whether these agents produce similar effects in animals, Silverman and Ho found that generalization (transfer) occurs when either R(−)-DOM or S(+)-DOM is administered to rats trained to discriminate (±)-DOM (1.5 mg/kg) from saline; only partial generalization occurs when the animals were administered doses of (±)-2,5-DMA [6]. In the course of our studies on the discriminative stimulus properties of hallucinogenic agents, we have recently examined the effect of minor molecular modification of the DOM structure on stimulus properties in order to determine which structural features are necessary to activity. The recent publication of Silverman and Ho [6] has prompted us to report the results of our work in this area.

METHOD

The animals used in this study were twenty-four 150-day-old male Sprague-Dawley rats. The animals weights were reduced to 80% of their expected free-feeding body weights by partial food deprivation.

Discrimination Training

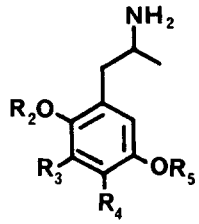
The discrimination training procedure for these animals has been previously reported [9]. In short, intraperitoneal (IP) administration of saline or (±)-DOM (1.0 mg/kg), 15 minutes prior to a variable 15-second (VI-15) schedule of reinforcement, served as the discriminative-cue for the correct (reinforced) lever. DOM or saline was administered on a double alternation schedule (i.e., 2 days DOM, 2 days saline). On every fifth day the rats' discrimination learning was assessed during an initial 2.5 min non-reinforced (extinction) period followed by a 12.5 min training session. Data that were collected during the extinction periods included total responses (expressed as mean responses/minute) and percent DOM-appropriate responding (number of responses on DOM-designated lever/total number of responses).

Substitution Tests

During substitution investigations, test sessions were interposed between discrimination training sessions. During these test sessions the animals were allowed 2.5 min of non-reinforced lever responding, and were then removed from the operant chambers. Substitution testing investigated the ability of the racemic DOM-cue to generalize to the (+)- and (−)-isomers of DOM, racemic 2,5-DMA and its (+)- and (−)-isomers, the 2,- and 5-demethyl derivatives of (±)-DOM, and the 3-methyl isomer of (±)-DOM. Doses of these compounds were administered IP in a random sequence with a 15-minute injection-time interval prior to the 2.5 min extinction test period.

Drugs

(±)-, (−)- and (+)-2,5-dimethoxy-4-methylphenylisopropylamine (DOM) hydrochloride were obtained from NIDA, (+)- and (−)-2,-5-dimethoxyphenylisopropylamine hydrochloride (2,5-DMA) were gifts from Dr. George M. Anderson while (±)-2,5-DMA hydrochloride was obtained



	R_2	R_3	R_4	R_5
2,5-DMA	CH_3	H	H	CH_3
DOM	CH_3	H	CH_3	CH_3
3-Me-2,5-DMA	CH_3	CH_3	H	CH_3
2-HMMP	H	H	CH_3	CH_3
5-HMMP	CH_3	H	CH_3	H

FIG. 1. Chemical structures of the molecular modifications of DOM used in the present study.

from NIDA, (±)-5-hydroxy-2-methoxy-4-methylphenylisopropylamine hydrochloride (5-HMMP) was a gift from Dr. Neal Castagnoli, (±)-2-hydroxy-5-methoxy-4-methylphenylisopropylamine hydrochloride (2-HMMP) and (±)-2,5-dimethoxy-3-methylphenylisopropylamine oxalate (3-Me-2,5-DMA were prepared as previously reported [2,3]. All drugs were dissolved in 0.9% aqueous sodium chloride and solutions were prepared immediately before use.

RESULTS AND DISCUSSION

Initial training studies, including duration of action, dose-response and ED_{50} for (±)-DOM (as the training drug), have been previously reported [9]. In this present study, we examined the ability of a racemic DOM stimulus response to generalize to the stereoisomers of DOM and to several related agents which represent molecular modifications of the DOM structure. These agents included R(−)-DOM, S(+)-DOM, the 4-demethylated (i.e., 2,5-DMA, as well as its optical isomers), 2-demethylated (i.e., 2-HMMP) and 5-demethylated (i.e., 5-HMMP) derivatives of (±)-DOM and a positional isomer of DOM where the 4-methyl group has been moved to the 3-position (i.e., 3-Me-2,5-DMA; Fig. 1.). The data obtained for these compounds are presented in Table 1. The (±)-DOM stimulus was found to generalize to R(−)-DOM, S(+)-DOM, (±)-2,5-DMA, R(−)-2,5DMA and (±)-2-HMMP, but not to S(+)-2,5-DMA, (±)-3-Me-2,5-DMA nor 5-HMMP. Where stimulus generalization occurred, it did so in a dose-related manner; except where disruption of behavior occurred, response rates were not significantly different under drug or non-drug (saline) conditions.

The results of the generalization study using the optical isomers of DOM are consistent with those of Silverman and Ho [6]; that is, the R(−)-isomer was found to be more active than either(±)-DOM or its S(+)-enantiomer. Table 1 shows that R(−)-DOM is twice as active as racemic DOM and at least eight-times more active than S(+)-DOM. Although Silverman and Ho found only partial generalization with (±)-2,5-DMA, we find that complete generalization occurs with both (±)-2,5-DMA and R(−)-2,5-DMA. Administration of 10 mg/kg of S(+)-2,5-DMA results in only 32% DOM-appropriate responding (Table 1), whereas higher doses result in complete disruption of behavior (i.e., no responding). The discrepency in the data for (±)-2,5-DMA may be related to the different training dose of (±)-DOM used in the two studies; however, it should be noted that the highest dose of (±)-2,5-DMA used in the Silverman and Ho study was only 8 mg/kg, whereas in the present study, generalization occurred at 10 mg/kg.

The behavioral effects produced by (±)-DOM appear to be related to the 4-position methyl group. The (±)-DOM stimulus does not generalize to 4-methylphenyl-isopropylamine [6], and removal of the 4-methyl group of DOM (i.e., (±)-2,5-DMA) results in a ten-fold decrease in activity. Apparently, the presence of both the methyl and the two methoxy groups are necessary for optimal activity. On the other hand, the location of this methyl group is also important; transposition of the methyl group of (±)-DOM from the 4- to the 3-position (i.e., 3-Me-2,5-DMA) essentially abolishes discriminative DOM-like activity. At about twenty times the ED_{50} dose of (±)-DOM, (±)-3-Me-2,5-DMA produces only 34 % DOM-appropriate responding. Many behaviorally-active phenylisopropylamines possess a characteristic 2,5-dimethoxy substitution pattern; although this pattern may be an important feature for activity, its influence is apparently tempered by the presence of a 3-methyl substituent.

In previous investigations, we have found that (±)-DOM and the tryptamine hallucinogen 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT) generalize to one another regardless of which agent is used as the training stimulus [4,9]. We have also reported that the 5-OMe DMT stimulus generalizes to (±)-2,5-DMA and (±)-2-HMMP, but not to (±)-5-HMMP [3,4]. The present study yields similar results; the (±)-DOM stimulus generalizes to the 2-demethylated derivative (±)-2-HMMP, but not to the 5-demethylated derivative (±)-5-HMMP. Apparently, demethylation of the 2-methoxy group of (±)-DOM results in a compound which retains DOM-like behavioral (discriminative) properties, while demethylation of the 5-methoxy group does not. It might be speculated that 0-demethylation decreases the lipophilicity of these DOM derivatives and that the 2-hydroxy compound is more likely than the 5-hydroxy compound to undergo internal hydrogen-bonding (making 2-HMMP less polar and better able than 5-HMMP to penetrate the blood-brain barrier). However, whereas such an explanation might be reasonable if 5-HMMP were inactive, the observation that 3.0 mg/kg of 5-HMMP produces behavioral disruption suggests that it might be centrally active but that it produces a stimulus response that is different from that of the training dose of (±)-DOM.

Four of the compounds included in this study have been previously evaluated in man [1, 5, 7, 8], and their human psychotomimetic potencies parallel their ED_{50} values as reported herein. That is, R(−)-DOM is twice as active as its racemate, which is, in turn, ten times more active than (±)-2,5-DMA; whereas R(−)-DOM is reported as being more than four times as active as its S(+)-enantiomer in man [5], the discrimination studies reveal that R(−)-DOM is eight times more active than S(+)-DOM.

In summary, the results of the present study indicate that R(−)-DOM and S(+)-DOM, as well as (±)-2,5-DMA, are capable, of producing a (±)-DOM-like stimulus response in rats, that the R(−)-isomers of DOM and 2,5-DMA are more

TABLE 1

RESULTS OF GENERALIZATION STUDIES USING (±)-DOM AS TRAINING DRUG

Drug	Dose (mg/kg)	N*	%DOM-appropriate Responding† (±SEM)	ED_{50} (mg/kg)‡	Mean Responses/ Minute† (±SEM)
(±)-DOM§	1.0	24/24	98%	0.44	14.8
R(−)-DOM	0.1	5/5	11% (3.3)		12.8 (2.7)
	0.2	5/5	43% (19.4)		11.6 (3.1)
	0.4	5/5	88% (12.2)		10.2 (2.9)
				0.21 (0.10–0.43)	
S(+)-DOM	1.0	5/5	27% (19.2)		10.0 (2.7)
	2.0	5/5	41% (16.4)		13.0 (3.5)
	3.0	5/5	79% (9.1)		12.2 (2.8)
	3.5	5/5	94% (3.7)		8.6 (1.7)
				1.70 (1.08–2.69)	
(±)-2,5-DMA	0.5	5/5	4% (2.2)		13.3 (1.0)
	1.0	5/5	6% (3.5)		18.2 (6.1)
	3.0	5/5	27% (9.4)		13.5 (3.9)
	5.0	5/5	35% (4.9)		15.0 (1.4)
	6.5	5/5	49% (17.7)		12.0 (3.3)
	8.0	5/5	56% (8.1)		14.8 (3.2)
	9.0	6/6	77% (17.2)		9.8 (1.1)
	10.0	5/5	95% (3.3)		16.2 (3.9)
				5.51 (3.98–7.63¶)	
R(−)-2,5-DMA	2.5	5/5	30% (20.0)		6.8 (1.5)
	3.5	5/5	51% (22.3)		9.8 (2.5)
	5.0	5/5	86% (9.7)		6.4 (1.2)
				3.25 (2.38–4.44)	
S(+)-2,5-DMA	10.0	5/5	32% (8.7)		10.6 (1.7)
	12.5	1/5	—#		
	15.0	0/5	—#		
(±)-3-Me-2,5-DMA	1.0	5/5	9% (3.1)		12.6 (4.9)
	3.0	4/5	12% (7.8)		17.0 (2.8)
	5.0	5/5	23% (15.8)		15.3 (1.1)
	8.0	3/5	34% (15.1)		15.7 (1.9)
(±)-2-HMMP	1.0	5/5	5% (3.9)		15.6 (2.2)
	1.5	5/5	46% (18.8)		14.8 (2.4)
	2.0	5/5	65% (16.5)		9.6 (2.7)
	3.0	4/5	94% (3.4)		14.5 (6.8)
				1.71 (1.25–2.35)	
(±)-5-HMMP	1.0	5/5	3% (2.0)		18.0 (3.6)
	2.0	4/5	12% (9.9)		14.5 (2.1)
	3.0	1/5	—#		
Saline§ (1.0 ml/kg)		24/24	5%		14.9

*Number of animals responding of animals tested.
†Data obtained during 2.5 minute test periods.
‡With 95% confidence limits.
§Data previously reported; included for comparative purposes.
¶The responses produced by the 0.5 and 1.0 mg/kg doses were not employed in determining the ED_{50} value.
#Disruption of behavior.

active than their racemates, that transposition of the 4-methyl group of (±)-DOM to the 3-position dramatically decreases DOM-appropriate responding, and that demethylation of the 2-methoxy group, but not the 5-methoxy group, of (±)-DOM results in retention of DOM-like behavioral properties.

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