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A Comparison of the Behavioral Effects of DOM Homologs

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GLENNON, R. A., R. YOUNG AND J. A. ROSECRANS. *A comparison of the behavioral effects of DOM homologs.* PHARMAC. BIOCHEM. BEHAV. 16(4) 557–559, 1982.—Twenty-four rats, trained to discriminate 1.0 mg/kg of (±)-DOM, i.e., (±)-2,5-dimethoxy-4-methylphenylisopropylamine, from saline under a VI-15 schedule of reinforcement, were challenged with a series of DOM homologs. The agents examined included the 4-ethyl (DOET), -propyl (DOPR), -butyl (DOBU), -tertiary butyl (DOTB) and -amyl (DOAM) derivatives as well as the R(−)- and S(+)-isomers of DOET. The (±)-DOM stimulus was found to generalize to all of the agents, except DOTB and DOAM, where only partial generalization occurred. The results suggest that the stimulus properties produced by the latter two compounds may differ from those of the remainder of the series. Furthermore, the ED_{50} values obtained, for those compounds to which the DOM-stimulus generalized, correlated significantly ($r^2=0.94$) with the human hallucinogenic potencies of these agents.

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

THE higher alkyl homologs of 2,5-dimethoxy-4-methylphenylisopropylamine (DOM), i.e., 4-ethyl (DOET), -propyl (DOPR), -butyl (DOBU), -tertiary butyl (DOTB), -amyl (DOAM), are behaviorally active in animals [3,8]. In addition, with the exception of DOTB, these agents are psychotomimetic in man [9,10]. The question has been raised, however, as to whether these agents are capable of producing similar behavioral effects [4]. Indeed, we have recently demonstrated that while stimulus generalization occurs between DOM and the hallucinogen 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT) (regardless of which of the two agents is used as the training drug) in tests of discriminative control of responding in rats [5,13], generalization does not occur when the DOM analogs are administered to the 5-OMe DMT-trained animals [4,6]. On the other hand, generalization does occur when DOET is administered to DOM-trained animals [11]. Furthermore, mescaline (to which 5-OMe DMT has been shown to generalize) also generalizes to both DOM and DOET [12]. Thus, while the discriminative effects produced by DOET may not be identical to those produced by 5-OMe DMT, they do appear to be similar to those of DOM. The aim of this current study was to determine whether or not generalization would occur when the DOM homologs were administered to rats trained to discriminate 1.0 mg/kg of racemic DOM from saline.

METHOD

Twenty-four male Sprague-Dawley rats were trained to discriminate 1.0 mg/kg (±)-DOM hydrochloride from saline in a two-lever operant task. This training has been discussed in detail [13], and these same twenty-four animals were used in the present study. Administration of DOM or saline 15 minutes prior to variable 15-second (VI-15) schedule of reinforcement served as the discriminative cue for the correct (reinforced) lever.

Substitution Tests

During the substitution investigations, test sessions were interposed between discrimination training sessions. During these test sessions, the animals were allowed 2.5 minutes of non-reinforced lever responding and were then removed from the operant chambers. The dose-response substitution tests assessed the percent "DOM-appropriate" responding produced by administration of the DOM homologs. Doses of compounds were administered intraperitoneally to groups of five to six animals, in a random sequence with a 15-minute injection-time interval prior to the 2.5-minute extinction session; during this 15-min time interval, the animals were returned to their home cages. For those compounds where generalization occurred, ED_{50} values were obtained from the dose-response data by the Litchfield-Wilcoxin method [7].

Drugs

(±)-2,5-Dimethoxy-4-methylphenylisopropylamine HCl (DOM) and, R(−)- and S(+)-2,5-dimethoxy-4-ethylphenylisopropylamine hydrochlorides (DOET) were obtained from NIDA. The hydrochloride salts of the remaining racemic derivatives, i.e., 2,5-dimethoxy-4-propyl-(DOPR), 2,5-dimethoxy-4-butyl- (DOBU), 2,5-dimethoxy-4-tertiary butyl-(DOTB), and 2,5-dimethoxy-4-amylphenylisopropylamine (DOAM) were gifts from Dr. A. T. Shulgin. Additional supplies of DOBU and DOTB were obtained from Dr. F. Benington. Solutions, in saline, were prepared fresh daily.

TABLE 1
RESULTS OF GENERALIZATION STUDIES

Compound*	N†	Dose (mg/kg)	%DOM-Appropriate Responding‡ (±SEM)	Responses/ min‡ (±SEM)	ED_{50} (mg/kg)§
(±)-2,5-DMA					5.51
(±)-DOM					0.44
(±)-DOET					0.23
(−)-DOET	5/5	0.05	34% (18.9)	11.6 (2.0)	
	5/5	0.125	51% (21.2)	9.0 (1.3)	
	6/6	0.25	68% (17.3)	12.2 (3.0)	
	6/6	0.30	95% (3.7)	11.3 (1.5)	0.09(0.04–0.20)
(+)-DOET	5/5	0.50	11% (5.0)	12.0 (3.1)	
	5/5	0.75	48% (15.4)	9.2 (1.8)	
	5/5	1.0	63% (13.7)	12.2 (2.7)	
	6/6	1.5	88% (7.8)	12.2 (3.5)	0.85(0.56–1.28)
(±)-DOPR	5/5	0.10	10% (5.5)	12.6 (3.2)	
	6/6	0.15	46% (17.4)	10.3 (1.3)	
	6/6	0.20	61% (19.1)	10.7 (1.8)	
	5/5	0.30	95% (3.5)	8.8 (1.6)	0.17(0.12–0.23)
(±)-DOBU	5/5	0.75	30% (18.5)	12.8 (1.7)	
	5/5	1.00	62% (21.1)	9.4 (1.8)	
	5/5	1.25	78% (5.6)	11.6 (2.0)	
	5/5	1.50	98% (1.9)	10.2 (1.5)	0.91(0.69–1.19)
(±)-DOTB	5/5	1.5	27% (18.8)	13.4 (4.1)	
	5/5	2.0	55% (23.3)	15.2 (4.0)	
	5/6	3.0	70% (20.0)	7.0 (1.4)	
	0/5	3.25	disruption		
	0/5	3.5	disruption		—
(±)-DOAM	5/5	0.50	0%	10.2 (1.5)	
	5/5	0.75	21% (19.7)	11.6 (1.1)	
	5/5	1.0	54% (20.4)	7.4 (3.0)	
	3/6	1.15	32% (25.6)	12.0 (1.0)	
	3/6	1.25	35% (21.8)	9.0 (3.9)	
	1/5	1.50	disruption		—
Saline (1 ml/kg)	24/24		5% (2.3)	14.9 (3.1)	—

*ED_{50} values for (±)-2,5-DMA, (±)-DOM and (±)-DOET have been reported ([13] and unpublished data).
†Number of animals responding/number of animals tested at that dose.
‡Data collected during 2.5-min extinction session.
§ED_{50} values followed by 95% confidence limits.

RESULTS AND DISCUSSION

We have previously reported that DOM serves as a discriminative stimulus in rats (ED_{50}=0.44 mg/kg) [13]. The (±)-DOM stimulus has been found to generalize to the stimuli produced by (±)-2,5-DMA and (±)-DOET (Glennon *et al.*, article in preparation). This present study reveals that generalization also occurs to R(−)-DOET, S(+)-DOET, (±)-DOPR and (±)-DOBU. On the other hand, administration of (±)-DOTB and (±)-DOAM results in only partial generalization (Table 1). Response rates, other than when disruption of behavior occurred, were not significantly different under drug or non-drug (saline) conditions.

Though psychoactive in man, DOPR, DOBU and DOAM have not been sufficiently studied to allow a qualitative comparison of their effects [9,10]. Nevertheless, DOM, DOET and DOPR are approximately similar in potency, with DOBU and DOAM being two to ten times less active [10]; DOTB is without central effect at doses of up to 25 mg [2]. In animal studies, DOPR and DOBU were found to be somewhat more active than DOM and DOET in a modified Sidman Avoidance paradigm, while DOTB and DOAM were essentially inactive [8]. Geyer *et al.* [3], found DOM, DOET and DOPR to be approximately equipotent in increasing tactile startle response amplitudes in rats. The 4-unsubstituted derivative 2,5-dimethoxyphenylisopropylamine (2,5-DMA), as well as DOTB and DOAM, were inactive; while DOBU increased startle response amplitude, the authors comment that the results were not statistically significant [3].

In all three studies, DOM, DOET, DOPR and DOBU display some activity, while DOTB is inactive. The amyl derivative (DOAM) is weakly active in humans but inactive

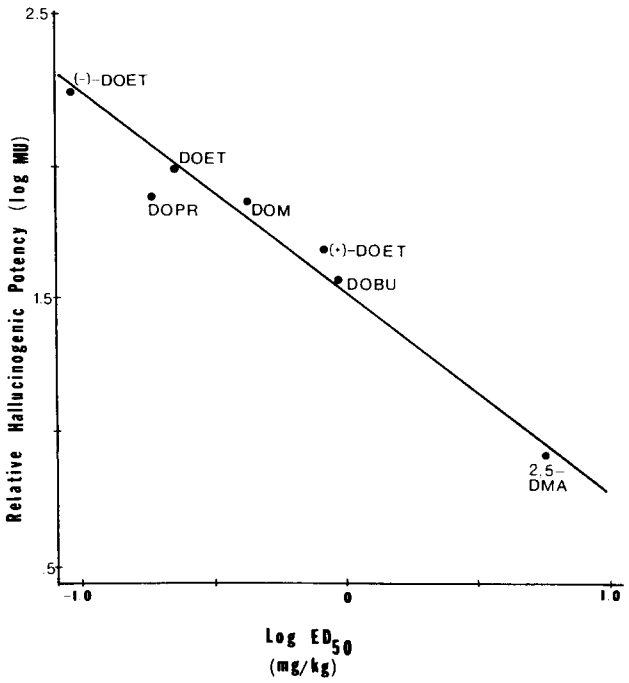

FIG. 1. Relationship between relative human hallucinogenic potency (MU=Mescaline Units) and the ED_{50} as determined using the discrimination paradigm. The human data, except for the isomers of DOET [1] are from reference [9].

in the animal studies. The results of the present study generally agree with these previous studies. With respect to potency, DOPR≥DOET>DOM>DOBU. Both DOTB and DOAM produce stimulus effects which may differ from either those of DOM or 5-OMe DMT.

With respect to human data, DOM is twice as active as DOBU and ten-times more active than 2,5-DMA as a hallucinogenic agent [10]. Similar results were obtained in the present study. In fact, the relationship between human hallucinogenic potency and the ED_{50} values as determined in generalization studies (using DOM as the training drug) are highly significant (Fig. 1).

One of the difficulties encountered in studying the mechanism of action and structure activity relationships of hallucinogenic agents is that information is lacking regarding similarity of effect. Indeed, it has been shown that various phenalkylamine derivatives produce dissimilar effects [6]. Geyer *et al.* [3], have questioned the premise that hallucinogens comprise a distinct category of drugs which share some common effect. They further comment that various agents are included in this class on the basis of subjective reports of humans, often with little or no rigorous observation [3]. The results of this study suggest that DOET, DOPR and DOBU, like 2,5-DMA and 5-OMe DMT, are apparently capable of producing stimulus effects in rats similar to those of the training drug DOM. On the other hand, the stimulus effects produced by DOTB and DOAM appear to be somewhat different. Continued studies of this sort should allow for a more complete classification of the entire class of psychotomimetic phenalkylamines with respect to whether or not they produce effects which are "DOM-like" in animals.

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