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INDOLEALKYLAMINE AND PHENALKYLAMINE HALLUCINOGENS

EFFECT OF α-METHYL AND *N*-METHYL SUBSTITUENTS ON BEHAVIORAL ACTIVITY

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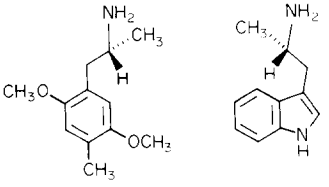
Abstract—Animals (rats), trained to discriminate the hallucinogenic agent 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from saline in a two-lever operant procedure, were challenged with various doses of several indolealkylamine and phenalkylamine derivatives. In both series, the α-methyl analogs were found to be more active than either their *N*-methyl or α-demethyl counterparts. Furthermore, when the activities of the optical isomers of DOM were compared with the activities of *S*-(+) and *R*-(−)-α-methyltryptamine (α-MeT), it was found that the more potent isomer of α-MeT (i.e. *S*) possessed the opposite absolute configuration of the more potent isomer of DOM (i.e. *R*). With respect to the mechanism of action of these agents, these findings are not inconsistent with a common site hypothesis.

We have reported previously that hallucinogenic derivatives of phenalkylamine and indolealkylamine possess a significant affinity for the serotonin (5-HT) receptors of the isolated rat fundus preparation [1, 2], and that these agents may interact with 5-HT receptors in such a manner as to share common aromatic and amine sites [3]. For example, terminal amine methylation, in either series, results in a 2- to 3-fold decrease in affinity [1, 2]. However, with respect to the phenalkylamines, optimal hallucinogenic activity is usually associated with a primary amino group (i.e. one which does not bear an alkyl substituent), whereas active indolealkylamine hallucinogens usually possess a terminal amine that is alkylated [4]. This apparent inconsistency does not support a mechanism of action which involves interaction at a common site; however, this situation has not been examined thoroughly.

Certain α-methyl derivatives of phenalkylamines (i.e. phenylisopropylamines) and of indolealkylamines (i.e. α-methyltryptamines) are also hallucinogenic in man [4, 5]. These latter derivatives possess a chiral center and, therefore, are capable of existing as optical isomers. If, indeed, phenylisopropylamine and α-methyltryptamine hallucinogens interact at a common site, in a manner such as that proposed by Kang and Green [6], it might be anticipated that the stereochemistry of the more potent isomer in one series should be opposite that of the other series in order to achieve a similar spatial orientation (see Fig. 1). In the few cases studied, the *R*-(−)-isomers of hallucinogenic phenylisopropylamines possess a greater 5-HT receptor affinity than their *S*-(+)-enantiomers [7]; furthermore, in man, the *R*-(−)-isomers are usually more potent than either their racemates or *S*-(+)-isomers [8]. While we have shown recently that *S*-(+)-α-methyltryptamine possesses 10 times the affinity of *R*-(−)-α-methyltryptamine [7], the behavioral activity of these isomers, as compared to the activity of the isomers of a phenylisopropylamine derivative, has not yet been reported.



R-(−)-DOM *S*-(+)-α-MeT

Fig. 1. Structures showing the absolute configurations of *R*-(−)-DOM and *S*-(+)-α-MeT.

Using a discriminative stimulus paradigm, with rats as subjects, and the hallucinogenic agent 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM; 1 mg/kg) as the training-drug, the aim of the present study was to challenge the above-mentioned tenets of a common site hypothesis. To this extent, it was first necessary to determine if the DOM-stimulus response would generalize to racemic α-methyltryptamine. Generalization studies were also performed using several related derivatives in both the phenalkylamine and indolealkylamine series in order to determine the relative effect and importance of *N*-methyl and α-alkyl substitution on behavioral activity.

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METHODS

Animals. The animals used in this study were 30 male Sprague–Dawley rats. The animals were housed in individual cages and maintained at approximately 80% of the expected free-feeding weight by partial food deprivation. Water was freely available in the home cage.

Apparatus. Standard operant chambers (Coulbourn model E10-10), housed within light-attenuating outer chambers, were used. Each chamber contained two levers that were mounted at opposite ends of one wall. A single dipper that delivered approximately 0.01 ml of sweetened condensed milk (diluted 2:1 with water) was positioned between the two levers. All programming and recording of data were done by solid-state and electromechanical equipment located in the same room.

Discrimination procedure. Rats were initially trained to respond on a fixed-ratio 1 (FR-1) schedule of reinforcement on one lever, with the other lever removed from the chamber. The schedule of reinforcement was gradually increased from FR-1 to a variable interval 15-sec (VI-15s) schedule of reinforcement on each lever independently. Lever-press training on VI-15s continued until rates of responding stabilized (approximately 18.7 responses/min). At this point drug discrimination training was begun.

Rats were injected intraperitoneally (i.p.) with either racemic DOM (1.0 mg/kg) or its vehicle (saline) 15 min before each session and were placed in the chambers with both levers present. For half of the rats, responding on the right lever, after drug administration, was reinforced; responding on the left lever after drug injection was reinforced for the other half. For all rats, responding on the non-drug lever was reinforced after administration of the injection vehicle. Training sessions were 15 min long. Saline or DOM was administered on a double alternation schedule (i.e. 2 days saline, 2 days DOM). On every fifth day, the discrimination learning of the rats 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 responses/min) and percent responding on the DOM-appropriate lever (number of responses on DOM-designated lever/total number of responses × 100).

Substitution tests. During substitution investigations, test sessions were interposed among discrimination training sessions. During these test sessions, the animals were allowed 2.5 min with no reinforcement for lever responding and were then removed from the operant chambers. An odd number of training sessions, generally three, separated any two substitution test sessions. Substitution tests investigated the ability of the animal to generalize the racemic DOM-stimulus response to various indolealkylamine and phenalkylamine derivatives. Doses of these compounds were administered i.p. in a random sequence with a 15-min injection-time interval prior to the 2.5-min extinction test period.

Drugs. Racemic, *R*-(−)- and *S*-(+)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane hydrochloride (DOM) were gifts from NIDA. Tryptamine hydrochloride was obtained from the Regis Chemical Co., Morton Grove, IL. Racemic, *R*-(−)- and *S*-(+)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminobutane hydrochloride (i.e. the α-ethyl homolog of DOM, or α-EH DOM) (BL-3912: lot numbers 11609-21, CD76-318 and 11709-14 respectively) were gifts from Dr. Richard A. Partyka of Bristol Laboratories, Syracuse, NY. 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminoethane hydrochloride (DM-DOM), as well as its *N,N*-dimethyl derivative (DD-DOM), were prepared according to literature procedures [9]. The remaining compounds have been synthesized previously in our laboratory (i.e. α-methyltryptamine hydrochloride, *N*-monomethyl DOM hydrochloride, 5-methoxytryptamine, α-ethyltryptamine acetate and *N,N*-dimethyltryptamine hydrogen oxalate) as a result of earlier studies. See Fig. 2 for structures. (±)-α-Methyltryptamine, as the free base, was resolved by treatment with *d*-(+)-10-camphorsulfonic acid; the salt was recrystallized several time from absolute ethanol and had the following properties: m.p. 233–234° (lit. [10] m.p. 236–237°); $[\alpha]_D^{24} = +29.3°$ (absolute ethanol) (lit. [10] $[\alpha]_D^{21.5} +27°$). This salt was converted to the free base by treatment with aqueous sodium hydroxide. The crude base was then recrystallized from ethylacetate/hexane to give *S*-(+)-α-MeT as colorless prisms, m.p. 128–129° (lit. [10] m.p. 128°). The optical rotation of this free base, $[\alpha]_D^{26} = +33.1$ (95% ethanol), is consistent with that reported earlier by Vane *et al.* ($[\alpha]_D^{?} = +34.7°$ [11]) and by Repke and Ferguson ($[\alpha]_D^{25} = +34.9°$ (methanol [12]). *R*-(−)-α-MeT was prepared in a similar manner: $[\alpha]_D^{26} = -30.1°$ (95% ethanol) (lit. [12] $[\alpha]_D^{25} = 32.1°$, methanol). Optical rotations were measured using a Perkin–Elmer model 141 polarimeter, and melting points were determined on a Fisher–Johns melting point apparatus.

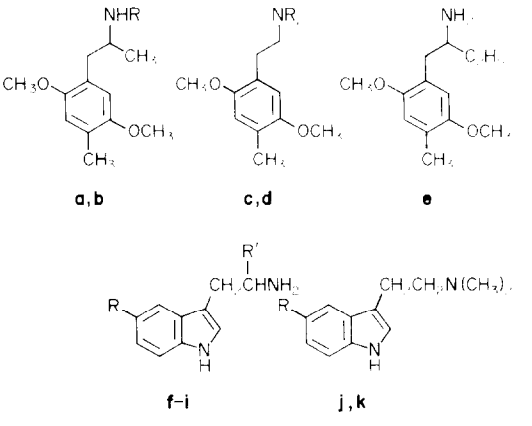

Fig. 2. Structures of agents used in this study: (**a**) DOM, R = H, (**b**) *N*-Me DOM, R = CH_3, (**c**) DM-DOM, R = H, (**d**) DD-DOM, R = CH_3, (**e**) α-EH DOM, (**f**) α-MeT, R = H, R′ = CH_3, (**g**) tryptamine, R = R′ = H, (**h**) 5-OMeT, R = OCH_3, R′ = H, (**i**) α-EtT, R = H, R′ = C_2H_5, (**j**) DMT, R = H, and (**k**) 5-OMe DMT, R = OCH_3.

All drugs were dissolved in sterile saline with the exception of 5-methoxytryptamine and *S*-(+)- and

R-(−)-α-methyltryptamine; these latter three compounds were initially dissolved in an equivalent of 0.1 N hydrochloric acid and were then diluted with sterile saline to the desired concentration. All solutions were prepared fresh daily.

RESULTS

Rats were trained to discriminate DOM (1.0 mg/kg) from saline administration. Preliminary studies, including duration of action, dose–response and ED_{50} for (±)-DOM, have already been reported [13]. These same DOM-trained animals were employed for this present study. For the purpose of this study, new dose–response data were obtained for (±)-DOM; the re-determined ED_{50} for (±)-DOM was found (Table 1) to be identical to that which we had reported earlier [13]. As shown in Table 1, DOM-stimulus generalization occurred to all of the phenalkylamine derivatives except the *S*-(+)-isomer of the α-ethyl homolog of DOM [i.e. *S*-(+)-α-EH DOM]. Stimulus generalization was also observed for doses of (±)- and *S*-(+)-α-methyltryptamine (α-MeT), (±)-α-ethyltryptamine (α-EtT), and *N*,*N*-dimethyltryptamine (DMT), but not for *R*-(−)-α-MeT, tryptamine or 5-methoxytryptamine (5-OMeT). At the highest dose tested (25 mg/kg), tryptamine produced only 13% DOM-appropriate responding. At low doses (1.0 to 2.25 mg/kg), 5-OMeT produced saline-like responding; at higher doses of 5-OMeT (>2.5 mg/kg), disruption of behavior (no responding) was observed. Both *S*-(+)-α-EH DOM and *R*-(−)-α-MeT produced partial generalization (at doses of 14.5 and 3.25 mg/kg respectively); attempts to increase the dose beyond that which resulted in partial generalization resulted in complete disruption of behavior. Where generalization occurred, it did so in a dose-related manner; response rates were not significantly different under drug or non-drug (saline) conditions except where complete disruption of behavior occurred.

DISCUSSION

Occurrence of stimulus generalization suggests that a challenge-drug is capable of producing behavioral (discriminative stimulus) effects similar to those produced by a particular training-drug. A comparison of ED_{50} values (Table 1) reveals that racemic α-methyltryptamine and *S*-(+)-α-methyltryptamine produced DOM-like effects with the latter being approximately twice as potent as the racemate. Administration of *R*-(−)-α-MeT, on the other hand, did not substitute completely for the DOM-stimulus response. Consistent with a common site hypothesis, the active isomer of α-MeT possesses the opposite absolute configuration (i.e. *S*) of the more active isomer of DOM (i.e. *R*). Homologation of the α-substituent from methyl to ethyl in either series (i.e. α-EH DOM and α-EtT) resulted in a significant decrease in activity. Nevertheless, a greater activity of the α-ethyl homolog of DOM still appeared to reside with the *R*-(−)-isomer.

Administration of the α-demethyl derivative of DOM (i.e. DM-DOM) to the DOM-trained animals revealed that removal of this methyl group resulted in a 3-fold decrease in potency. Interestingly, the corresponding primary amine derivative of α-MeT (i.e. tryptamine) produced saline-like responding even at five times the ED_{50} dose of (±)-α-MeT. Stimulus generalization occurs between DOM and 5-methoxy-*N*,*N*-dimethyltryptamine (5-OMe DMT) regardless of which of the two agents is used as the training-drug [13, 21]. However, administration of 5-OMeT, the primary amine derivative of 5-OMe DMT, produced saline-like responding at low doses; administration of higher doses of 5-OMeT resulted in disruption of behavior. In two instances then, the primary amine derivatives of indolealkylamines were essentially inactive (i.e. incapable of producing DOM-like effects), while DM-DOM was active. While this finding may argue against the common site hypothesis, several additional factors should be considered. Vogel and co-workers [22, 23] have found that intraperitoneal doses of tryptamine and its 5-methoxy derivative penetrate the rat blood–brain barrier to an extremely small extent. Furthermore, at a dose of 50 mg/kg, 5-OMeT produces a very small brain to blood plasma ratio, a ratio similar to that observed after administration of 5-hydroxy-*N*,*N*-dimethyltryptamine (bufotenine) or serotonin [24]. These results are explained, but only in part, by the rapid metabolism of tryptamine and 5-OMeT. These same investigators have found that certain primary amine derivatives of phenalkylamines, both phenylisopropylamines and phenethylamines, (although DM-DOM, itself, was not examined in this study) are far better able, than primary α-unsubstituted tryptamines, to penetrate the blood–brain barrier [22, 23]. Thus, tryptamine and its 5-methoxy derivative may appear to be relatively inactive by virtue of their failure to achieve significant brain levels. In any event, removal of the α-methyl group of DOM or α-MeT resulted in decreased activity.

Methylation of the terminal amine of DOM (i.e. *N*-Me DOM), as well as dimethylation of the α-demethyl derivative DM-DOM (i.e. DD-DOM), resulted in compounds which were less active than their parent. This same effect was seen in the indolealkylamine series, with DMT being somewhat less active than (±)-α-MeT (Table 1).

In considering the results of this study, it would be gratifying and, indeed, more meaningful, if there existed a correspondence with human hallucinogenic activity. Of the ten different compounds examined, human data are available for five, as well as for the *R*-(−)-isomer of DOM. A plot of human hallucinogenic dose versus ED_{50}, from Table 1, reveals a significant correlation ($r^2 = 0.99$) between the two activities (Fig. 3). Tryptamine is essentially inactive in man [25], as it was in the discrimination study. In clinical trials (as communicated by Winter [26], α-EH DOM, in doses of up to 270 mg in normal human subjects, produced euphoria and other LSD-like effects but failed to reveal hallucinogenic activity. Interestingly, however, complete stimulus generalization was observed when α-EH DOM was administered to animals trained to discriminate LSD from saline [26].

In both the phenalkylamine and indolealkylamine series, the most active agent was the amine-unsubstituted α-methyl derivative. The *N*-methyl analogs

Table 1. Results of generalization studies

Agent	Dose (mg/kg)	N*	% DOM-appropriate responding† (± S.E.M.)	Mean responses/min† (± S.E.M.)	ED_{50}‡ (mg/kg)	Human hallucinogenic dose§ (mg)
(±)-DOM	0.2	5/5	13 ± 5.9	10.6 ± 1.7		
	0.4	5/5	40 ± 1.3	15.2 ± 3.3		
	0.6	5/5	59 ± 10.1	14.8 ± 3.7		
	0.8	5/5	79 ± 10.6	12.0 ± 2.4		
	1.0	30/30	97 ± 1.3	15.1 ± 2.6	0.44 (0.29–0.69)	2.0–5.0‖
R-(−)-DOM					0.21¶	1.0–2.5**
S-(+)-DOM					1.7¶	
(±)-*N*-Me DOM	3.0	4/5	9 ± 5.3	12.5 ± 2.3		
	3.5	5/5	28 ± 19.6	11.2 ± 2.9		
	4.0	4/5	48 ± 16.2	10.8 ± 1.9		
	4.5	5/5	68 ± 8.9	14.4 ± 2.4		
	5.0	5/5	89 ± 6.0	13.0 ± 2.9	3.99 (3.42–4.66)	20–50††
R-(−)-*N*-Me DOM	1.5	5/5	20 ± 8.4	13.0 ± 1.9		
	2.5	5/5	46 ± 9.7	11.8 ± 1.7		
	4.0	5/5	71 ± 12.4	10.5 ± 1.1		
	4.25	4/5	83 ± 10.2	12.2 ± 1.6	2.59 (1.74–3.87)	
DM-DOM	0.5	5/5	14 ± 8.5	13.0 ± 1.1		
	1.25	5/5	37 ± 17.0	12.6 ± 1.2		
	2.0	5/5	68 ± 17.7	15.0 ± 1.1		
	4.0	4/5	96 ± 1.9	14.0 ± 1.3	1.31 (0.67–2.56)	10–15‡‡
DD-DOM	1.0	5/5	10 ± 4.3	12.6 ± 1.0		
	3.0	5/5	8 ± 4.2	12.7 ± 1.2		
	5.0	5/5	47 ± 15.1	12.4 ± 2.4		
	7.0	4/5	63 ± 15.5	11.3 ± 1.1		
	8.5	4/5	80 ± 16.0	10.0 ± 1.8		
	10.0	1/5	§§		5.37 (2.79–10.31)	
(±)-α-EH DOM	5.0	4/5	35 ± 9.8	14.0 ± 1.2		
	7.0	5/5	59 ± 12.4	10.2 ± 1.6		
	9.0	4/5	60 ± 16.8	11.3 ± 4.3		
	10.0	3/5	73 ± 10.5	5.0 ± 1.0		
	10.5	4/6	80 ± 7.9	10.2 ± 2.3		
	11.0	4/6	93 ± 3.5	8.9 ± 4.2	6.44 (4.71–8.81)	‖‖
R-(−)-α-EH DOM	3.0	5/5	26 ± 18.8	13.8 ± 2.4		
	5.0	5/5	50 ± 12.5	16.4 ± 2.3		
	7.0	5/5	77 ± 10.2	13.4 ± 1.6		
	8.0	4/5	84 ± 13.1	13.3 ± 3.9	4.59 (3.13–6.73)	
S-(−)-α-EH DOM	7.0	5/5	29 ± 16.1	10.4 ± 2.4		
	10.0	5/5	37 ± 15.5	10.6 ± 1.5		
	12.5	4/5	38 ± 14.1	11.8 ± 1.0		

	13.75	4/5	58 ± 11.4	13.0 ± 2.1		
	14.5	3/5	59 ± 8.5	9.3 ± 1.4		
	15.0	1/5	§§			
(±)-α-MeT	2.0	5/5	23 ± 15.1	11.0 ± 1.8		
	3.0	5/5	48 ± 21.4	11.6 ± 2.2		
	4.5	4/5	59 ± 20.5	10.8 ± 1.9		
	5.0	5/5	72 ± 6.6	10.5 ± 1.6		
	5.25	5/5	95 ± 3.4	10.4 ± 2.0	3.13 (2.29–4.27)	20–50¶¶
R-(−)-α-MeT	2.0	5/5	13 ± 5.6	9.0 ± 1.6		
	2.75	5/5	42 ± 14.6	13.0 ± 2.5		
	3.0	4/5	53 ± 14.8	9.0 ± 1.9		
	3.25	3/5	61 ± 5.8	7.5 ± 1.2		
	3.5	0/5	§§			
S-(+)-α-MeT	1.25	4/4	22 ± 12.5	16.0 ± 1.9		
	1.75	5/5	48 ± 14.2	11.9 ± 1.8		
	1.85	5/5	59 ± 21.6	12.3 ± 1.5		
	2.0	5/5	84 ± 8.0	10.8 ± 1.9	1.64 (1.34–2.00)	
Tryptamine	7.0	5/5	5 ± 2.0	12.0 ± 1.1		
	12.0	4/5	4 ± 3.1	11.0 ± 1.2		
	15.0	3/5	8 ± 3.3	10.0 ± 1.7		
	25.0	3/6	13 ± 12.7	9.7 ± 2.2		
5-OMeT	1.0	5/5	0	11.8 ± 1.9		
	2.0	5/5	18 ± 9.8	11.8 ± 1.9		
	2.25	3/5	12 ± 8.6	9.2 ± 1.6		
	2.5	2/5	§§			
	3.0	2/5	§§			
	4.0	1/5	§§			
(±)-α-EtT	4.5	4/5	27 ± 9.2	10.5 ± 2.1		
	6.0	4/5	40 ± 15.4	10.8 ± 1.6		
	8.0	4/5	60 ± 19.5	10.6 ± 1.7		
	10.0	4/5	78 ± 10.6	10.4 ± 1.4		
	11.0	3/5	84 ± 4.1	9.7 ± 2.4	6.62 (4.65–9.34)	
DMT	3.0	5/5	10 ± 10.0	10.4 ± 2.4		
	4.5	5/5	35 ± 6.8	12.6 ± 3.2		
	6.5	4/5	53 ± 23.1	13.3 ± 2.0		
	7.25	3/5	55 ± 19.8	11.3 ± 1.9		
	7.5	3/5	62 ± 24.0	9.3 ± 3.2		
	7.75	3/5	79 ± 10.4	10.0 ± 1.7		
	7.85	3/5	85 ± 7.8	9.8 ± 2.3		
	8.0	1/6	§§			
	10.0	0/5	§§		5.80 (4.24–7.79)	60***
Saline	1.0 (ml/kg)	30/30	4 ± 2.1	14.8 ± 3.1		

Notes to Table 1

* Ratio of number of animals responding to number of animals tested at that particular dose.
† Data obtained during a 2.5-min extinction session.
‡ The ED_{50} value is followed by 95% confidence limits.
§ Total mg dose.
‖ Human dose reported by Shulgin [8].
¶ ED_{50} Values previously reported [14]; included for comparative purposes.
** Shulgin [15] has reported that *R*-(−)-DOM is twice as active as (±)-DOM; therefore, one-half the reported dose for (±)-DOM has been used.
†† Data from Anderson *et al.* [16] and from Shulgin (personal communication).
‡‡ Data from Shulgin and Carter [17].
§§ Disruption of behavior.
‖‖ See text for discussion.
¶¶ Data from Murphree *et al.* [18], Hollister *et al.* [19], and Shulgin and Nichols [20].
*** Data from Kantor *et al.* [5].

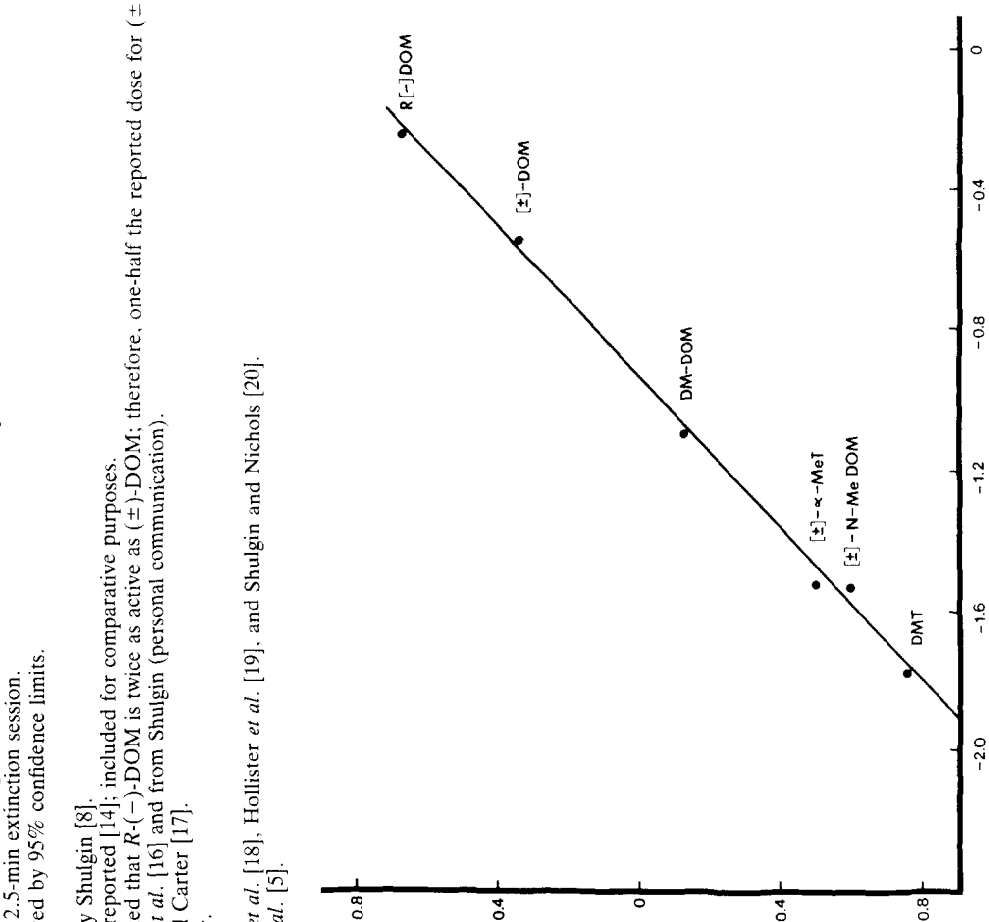

Fig. 3. Relationship between the human hallucinogenic dose (total mg dose) and the drug discrimination ED_{50} dose for those agents where data are available.

were less active, with the α-ethyl homologs having been the least active. The α-demethyl derivative of DOM (i.e. DM-DOM) was several-fold less active than DOM itself, while tryptamine, the α-demethyl derivative of α-MeT, was essentially inactive; nevertheless, α-demethylation resulted in similar trends in both cases. Previous attempts to explain the inactivity of tryptamine have focused on its inability to penetrate the blood–brain barrier. Where comparisons can be made, similarities exist between the results of this study and the results of human studies. Although parallel structural modifications resulted in parallel qualitative changes in activity within the two series, these differences in activity were not quantitatively similar. This may be explained on the basis of different routes and rates of metabolism or by the different distributional characteristics of phenalkylamines versus indolealkylamines.

The present investigation reveals that certain hallucinogenic derivatives of phenalkylamine (i.e. DM-DOM and its α-methyl and *N*-methyl derivatives) and indolealkylamine (i.e. α-methyl and *N*-dimethyl derivatives of tryptamine) produce similar behavioral (discriminative stimulus) effects in rats; the results obtained are not inconsistent with the idea that these agents might act via interaction with a common site.

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