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DOM-STIMULUS GENERALIZATION TO LSD AND OTHER HALLUCINOGENIC INDOLEALKYLAMINES

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Stimulus generalization studies were conducted using rats trained to discriminate 1.0 mg/kg of the phenalkylamine hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from saline in a two-lever operant procedure. The results suggest that certain indolealkylamine hallucinogens, including LSD and several α-methyltryptamine, N,N-dialkyltryptamine and β-carboline derivatives, are capable of producing stimulus effects similar to those produced by DOM. Furthermore, for twelve agents where human data are available, a significant correlation exists between discrimination-derived ED_{50} values and hallucinogenic potency.

Hallucinogenic agents Drug discrimination β-Carbolines Indolealkylamines LSD DOM

1. Introduction

Based on electronic and stereochemical considerations, Kang and Green (1970) have suggested that certain indolealkylamine and phenalkylamine hallucinogens might interact with a common receptor. Although there is some lack of agreement as to the spatial orientation by which this interaction might occur (Baker et al., 1973; Nichols et al., 1978), this hypothesis is supported, for the most part, by empirical data. For example, we have demonstrated that various indolealkylamine and phenalkylamine hallucinogens interact with the serotonin (5-HT) receptors of the isolated rat fundus preparation. These studies have included tryptamines, N-alkyltryptamines, α-alkyltryptamines, phenylisopropylamines, and, most recently, β-carbolines (Glennon and Gessner, 1979; Glennon et al., 1980). Furthermore, those hallucinogenic agents which are the most potent in man possess the highest 5-HT receptor affinities (Glennon and Rosecrans, 1982). Crucial to the 'common site hypothesis' is a demonstration that members of each of these classes of agents are capable of producing similar, i.e. common, behavioral effects in vivo. The phenalkylamine hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) serves as a discriminative stimulus in rats when paired with saline (Silverman and Ho, 1980; Young et al., 1981). DOM-stimulus generalization occurs upon administration of various hallucinogenic phenalkylamine derivatives and, in addition, there is a significant correlation between the discrimination-derived ED_{50} values for these agents and their human hallucinogenic potencies (Glennon et al., 1982a). Based on the 'common site hypothesis', it might be anticipated that the DOM stimulus will generalize to various indolealkylamine hallucinogens; this idea is supported, to some extent, by our previous demonstration of stimulus generalization between DOM and several such agents (Glennon et al., unpublished observations). The purpose of this present investigation was to examine an extended series of indolealkylamine hallucinogens and related com-

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TABLE 1

Results of generalization studies involving indolealkylamines.

Agent	Dose (mg/kg)	n [a]	% DOM-appropriate responding (±S.E.M.) [b]	Responses/ min (±S.E.M.)	Human hallucinogenic dose (mg)
DMT [c]	ED_{50} = 5.80				50-100 [f]
4-OMe DMT	2.0	5/5	31% (6.9)	13.8 (2.7)	–
	3.0	4/5	40%(15.2)	12.1 (1.8)	
	5.0	4/5	55%(18.6)	10.8 (2.1)	
	6.0	4/5	68% (8.5)	11.3 (1.2)	
	6.5	4/5	84% (6.2)	9.8 (1.2)	
	ED_{50} = 3.53 (2.01-6.20)				
4-Me DMT	1.0	5/5	0%	15.4 (2.6)	–
	1.5	5/5	27%(10.5)	11.6 (1.8)	
	2.5	4/5	49%(18.5)	10.5 (1.3)	
	3.5	4/5	63%(16.9)	10.5 (3.0)	
	4.25	3/5	76%(16.6)	10.3 (1.0)	
	4.50	3/5	81%(12.5)	12.6 (1.2)	
	6.0	1/5	[d]		
	7.0	0/5	[d]		
	ED_{50} = 2.49 (1.52-4.07)				
5-OMe DMT [e]	ED_{50} = 1.22				6 [g]
5-OMe Gramine	1.0	3/3	2% (1.7)	11.7 (2.6)	–
	3.0	4/4	4% (3.7)	9.3 (1.0)	
	6.0	3/4	2% (1.2)	10.2 (1.3)	
5-OMe 7-TMT	1.0	3/3	37%(15.1)	10.3 (3.4)	–
	1.25	4/4	59%(20.1)	11.3 (2.1)	
	1.5	4/5	89%(10.0)	9.3 (2.1)	
	2.0	2/3	100%	8.0 (1.5)	
	ED_{50} = 1.12 (0.83-1.50)				
6-OMe DMT	3.0	5/5	5% (1.8)	14.2 (2.1)	
	6.0	5/5	8% (5.8)	11.2 (1.4)	
	10.0	5/5	9% (4.3)	13.8 (1.2)	
7-Me DMT	4.0	5/5	30%(16.0)	14.8 (2.2)	–
	5.0	4/5	53%(18.4)	12.3 (1.5)	
	6.0	5/5	72% (8.1)	10.0 (1.7)	
	7.5	5/5	84% (6.7)	10.2 (1.2)	
	ED_{50} = 4.89 (3.60-6.64)				
DET	1.5	3/5	25%(17.7)	12.5 (1.2)	50-70 [h]
	3.0	3/5	39%(20.8)	9.3 (2.7)	
	3.25	5/5	68%(14.3)	10.5 (2.6)	
	3.50	4/5	86% (8.3)	9.5 (1.9)	
	4.0	1/5	[d]		
	ED_{50} = 2.45 (1.59-3.78)				
5-OMe DET	0.5	5/5	25%(12.7)	9.4 (1.0)	–
	1.0	3/5	68%(11.6)	9.3 (2.8)	
	1.5	4/5	90%(12.7)	11.0 (3.1)	
	ED_{50} = 0.75 (0.42-1.31)				
DPT	1.5	5/5	18%(10.8)	10.6 (1.6)	30-70 [i]
	2.5	5/5	55%(17.5)	12.4 (1.9)	
	3.0	4/5	83%(11.4)	8.5 (2.6)	
	6.0	2/5	[d]		
	ED_{50} = 2.20 (1.64-2.94)				

TABLE 1 (continued)

Agent	Dose (mg/kg)	n [a]	% DOM-appropriate responding (±S.E.M.) [b]	Responses/ min (±S.E.M.)	Human hallucinogenic dose (mg)
DIPT	1.5	5/5	7% (2.7)	10.2 (2.8)	20-50 [j]
	2.25	5/5	39% (8.5)	10.8 (2.0)	
	3.0	4/5	63%(19.0)	12.0 (3.2)	
	4.5	4/5	93% (6.3)	11.3 (2.3)	
	ED_{50} = 2.60 (1.82-3.71)				
5-OMe DIPT	0.5	3/3	18% (9.7)	11.7 (1.3)	6-10 [j]
	1.5	3/3	58%(25.8)	11.3 (3.3)	
	2.0	3/3	85%(13.5)	9.5 (2.7)	
	ED_{50} = 1.06 (0.52-2.17)				
(±)-α-MeT [c]	ED_{50} = 3.13				20-50 [k]
(±)-5-OMe α-MeT [c]	ED_{50} = 0.52				3 [g]
(+)-LSD	0.04	3/3	31%(10.7)	11.0 (1.5)	0.1 [l]
	0.08	5/5	75%(12.6)	11.3 (2.7)	
	0.10	3/3	93% (5.1)	12.7 (1.8)	
	ED_{50} = 0.052 (0.032-0.086)				
Harman	4.5	3/5	8% (6.4)	8.0 (1.3)	–
	5.25	3/5	14% (7.6)	7.8 (2.1)	
	6.0	1/5	–		
	9.0	0/5	–		
Harmine	4.0	3/5	25%(11.2)	9.0 (1.6)	–
	5.0	3/5	30% 99.5)	7.1 (1.5)	
	6.0	1/5	–		
	8.0	0/5	–		
Harmaline	5.0	5/5	36%(15.5)	8.9 (1.8)	100-300 [m]
	8.0	4/5	61%(17.3)	8.3 (2.7)	
	9.0	3/6	81%(10.7)	7.7 (1.5)	
	ED_{50} = 6.19 (4.04-9.49)				
6-OMe Harmalan	4.0	5/5	27% (4.7)	8.0 (1.8)	100 [m]
	5.0	6/6	46%(16.0)	10.2 (2.5)	
	6.5	4/5	71%(17.8)	8.5 (1.0)	
	7.0	5/5	81%(10.2)	12.4 (1.3)	
	8.0	1/6	–		
	ED_{50} = 5.13 (4.03-6.53)				

[a] n = Number of animals responding of the number of animals tested at a particular dose. [b] Where generalization occurred, ED_{50} values (mg/kg) are given; the ED_{50} value is followed by 95% confidence limits. [c] Data previously reported (Glennon et al., 1982b); ED_{50} value included for comparative purposes. [d] Disruption of behavior. [e] Data previously reported (Young et al., 1981); ED_{50} value included for comparative purposes. [f] Szara, 1956; Boszormenyi and Szara, 1958; Sai-Halasz, 1962; Gillin et al., 1976. [g] Kantor et al., 1980. [h] Boszormenyi et al., 1959; Szara et al., 1966. [i] Faillace et al., 1967; Soskin, 1975. [j] Shulgin and Carter, 1981. [k] Murphree et al., 1961; Hollister et al., 1960; Kantor et al., 1980. [l] Sankar, 1975. [m] Naranjo, 1967.

pounds, including tryptamine derivatives, LSD and several β-carbolines, in order to determine (a) if these agents can produce stimulus effects similar to those of DOM, and (b) whether, like with the phenylisopropylamine derivatives, a correlation exists between their ED_{50} values and their human hallucinogenic potencies.

2. Materials and methods

2.1. Subjects

The animals used in this study were 24 Sprague-Dawley male rats. The animals weights were reduced to 80% of their free-feeding weights by partial food deprivation. Animals had free access to water.

2.2. Apparatus

Commercially available operant chambers (Coulbourn Instruments), housed within sound and light attenuated outer chambers were used. Each chamber contained two levers mounted at the same end of the chamber. A single dipper that delivered 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.

2.3. Discrimination procedure

The drug discrimination training procedure for these animals has been reported previously (Young et al., 1981). Briefly, the rats were trained to discriminate racemic DOM (1.0 mg/kg) from saline using the two-lever operant choice task. In this procedure the administration of saline or DOM, 15 min prior to a variable interval 15-s (VI-15) 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 the various indolealkylamines. All agents were administered by intraperitoneal injection. For those compounds where generalization (transfer, substitution) occurred, ED_{50} values were determined from the dose-response data by the method of Litchfied and Wilcoxon (1949).

2.4. Drugs

Most of the agents employed in this study were previously synthesized in our laboratories and were on hand as a result of earlier investigations. These agents include N,N-dimethyltryptamine (as the hydrogen oxalate or HOx salt) (DMT), 4-methoxy-N,N-dimethyltryptamine HOx (4-OMe DMT), 4-methyl-N,N-dimethyltryptamine HOx (4-Me DMT), 5-methoxy-N,N-dimethyltryptamine HOx (5-OMe DMT), 6-methoxy-N,N-dimethyltryptamine HOx (6-OMe DMT), 7-methyl-N,N-dimethyltryptamine HOx (7-Me DMT), 5-methoxy-N,N-diethyltryptamine HOx (5-OMe DET), α-methyltryptamine hydrochloride (α-MeT), and 5-methoxy-7,N,N-trimethyltryptamine HOx (5-OMe-7-TMT). (+)-Lysergic acid diethylamide tartrate monomethanolate (LSD) was a gift from NIDA and (±)-5-methoxy-α-methyltryptamine hydrochloride (5-OMe α-MeT) was a gift from the Psychopharmacology Research Branch of NIMH. N,N-Diethyltryptamine (DET), N,N-dipropyltryptamine (DPT) and N,N-diisopropyltryptamine (DIPT), as their hydrochloride salts, were synthesized according to the method of Brimblecombe et al. (1964) and 5-methoxy-N,N-diisopropyltryptamine was prepared according to Shulgin and Carter (1981). All of the β-carboline derivatives were obtained from Sigma Chemical Company (Saint Louis, Missouri). 5-Methoxygramine (i.e., 3-dimethylaminomethyl-5-methoxy-indole) was obtained from Aldrich Chemical Company (Milwaukee, Wisconsin). Solutions were prepared fresh daily in sterile saline.

3. Results

The DOM (1.0 mg/kg) stimulus was found to generalize to LSD and to all of the tryptamine derivatives except 6-OMe DMT. The latter agent, at 10 mg/kg, elicited saline-like responding; higher doses were not tested. Both harmaline and 6-OMe harmalan produced DOM-appropriate responding, while harmine and harman produced disruption of behavior at 6.0 mg/kg. Where stimulus generalization occurred, it did so in a dose-related manner; ED_{50} values are shown in table 1. Response rates were not significantly different under drug or non-drug (i.e., saline control) conditions except where disruption of behavior (i.e., no responding) occurred. All four β-carbolines produced body

tremor at all doses; this was particularly noticeable for harmine and harman where, even at the lowest doses tested, two of five animals were disrupted and did not respond. 5-Methoxygramine, at the highest dose tested, produced saline-like responding; higher doses were not tested due to solubility problems.

Within the dimethyltryptamine series, with the exception of 6-OMe DMT, all agents were more active than the parent compound. 6-OMe DMT was essentially inactive at the highest dose tested; substitution at either the 4- or 7-position by a methyl group enhanced activity. Shortening the ethylamine sidechain of 5-OMe DMT by one methylene unit (i.e., 5-OMe gramine) resulted in a dramatic decrease in activity. Comparing the three

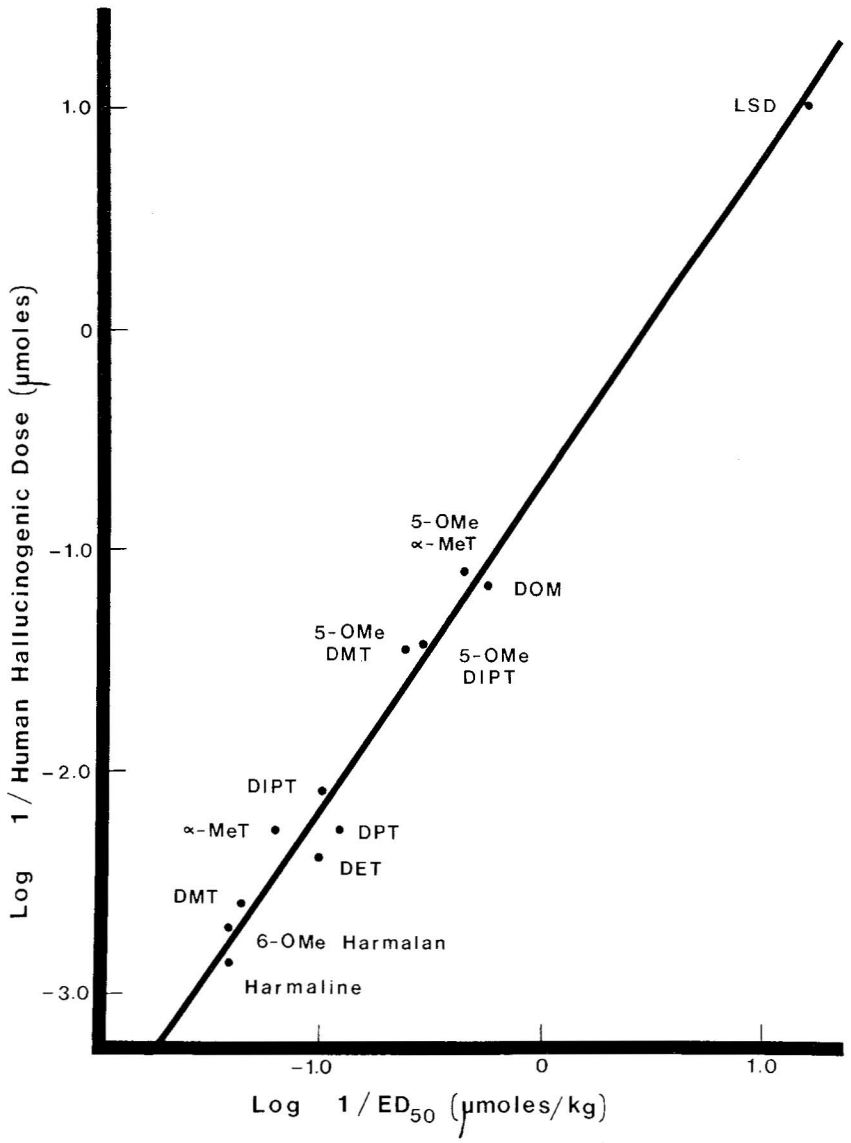

Fig. 1. A plot of human hallucinogenic potency (log 1/total human dose in μmol) against ED_{50} values (log $1/ED_{50}$ in μmol/kg) for those agents where data are available (where dose ranges are given for human data in table 1, the arithmetic mean was used).

methoxy-substituted derivatives of DMT, activity increased in the order 6-OMe < 4-OMe < 5-OMe. All three N,N-dialkyl derivatives (i.e. DET, DPT, DIPT) were more active than DMT; 5-methoxy substitution further enhanced activity such that 5-OMe DET and 5-OMe DIPT were found to be slightly more active than 5-OMe DMT. Harmaline and 6-OMe harmalan were approximately comparable in potency to DMT. LSD was, by far, the most potent agent of the entire series.

4. Discussion

In tests of discriminative control of responding, it is assumed that agents which produce similar subjective effects in humans will possess similar discriminative properties in animals. Although the exact nature of the stimulus cues produced by these agents is not fully understood, this hypothesis has received considerable support. DOM-stimulus generalization has been found to occur upon administration of a series of phenalkylamine hallucinogens (Glennon et al., 1982a), as well as for the indolealkylamine hallucinogen 5-methoxy-N,N-dimethyltryptamine (Young et al., 1981). Silverman and Ho (1978), although they examined only one dose, found that LSD produces stimulus effects similar to DOM in DOM-trained animals. The results of this present study suggest that sixteen indolealkylamines, including LSD, several tryptamine derivatives and two β-carbolines, are capable of producing stimulus effects similar to those of 1.0 mg/kg of DOM. Although these findings shed little light on the structural conformation or spatial orientation with which these agents might interact with a particular receptor, they are, nevertheless, consistent with and supportive of th 'common site hypothesis'.

The human potency of hallucinogenic agents is necessarily difficult to measure, and is subject to a certain amount of variability, due to the subjective nature of the effects produced by such agents. Furthermore, some human studies may have been conducted under less than optimal conditions, e.g. use of limited subject populations. Thus, it should be realized that, in general, human hallucinogenic data may reflect such shortcomings. Nonetheless, using previously reported human values which, on a molar basis, vary over nearly four orders of magnitude, there exists a direct correlation between hallucinogenic potency (for the twelve compounds where data are available) and discrimination-derived ED_{50} values (fig. 1). This finding strenghtens and extends a similar relationship already reported for a series of phenalkylamine derivatives (Glennon et al., 1982a). For those agents where human data are unavailable, the results of this study are, in general, consistent with the results of other animal studies. For example, 5-OMe DET is more active than 4-OMe DMT, which is, in turn, more active than 6-OMe DMT in disrupting conditioned avoidance behavior in rats (Gessner et al., 1968); in a similar test, 5-OMe gramine was found to be much less active than 5-OMe DMT (Gessner et al., 1961).

Three indolealkylamines, LSD (Sankar, 1975), DPT (Soskin, 1975) and harmaline (Naranjo, 1973), have been extensively evaluated as adjuncts to psychotherapy. These and other hallucinogenic agents can produce a variety of syndromes which are characterized by distinctive behavioral subtleties that may be clearly different from one another; in addition, certain agents produce distinguishing somatic effects (e.g. nausea and other side-effects). In fact, Naranjo (1973) has commented that a given agent may produce different effects in the same individual on different occasions of administration. Nevertheless, on the basis of their stimulus properties, all of the agents in fig. 1 apparently produce qualitatively similar effects in rats. Whether rats are more sensitive to the effects that are common to these agents, or whether they lack the repetoire of human behavioral experienes necessary to distinguish their subtle differences, they are able to both qualitate and quantitate the activities of various hallucinogenic agents such that the results parallel data obtained from human studies.

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