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BEHAVIORAL PROPERTIES OF PSYCHOACTIVE PHENYLISOPROPYLAMINES IN RATS

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Rats were trained to discriminate injections of 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT, 3.0 mg/kg), a hallucinogenic agent for which a serotonergic mechanism has been implicated, from saline in a two-lever drug discrimination task. After reliable levels of accuracy (≥85%) were attained, the ability of the 5-OMe DMT cue to generalize to 36 substituted phenylisopropylamines (or their optical isomers) was assessed. The results reveal that, in general, the challenge compounds could be differentiated into three broad categories: Those that produced 5-OMe DMT-appropriate responding (generalization), those that produced partial 5-OMe DMT-appropriate responding (partial generalization) and those that produced negligible 5-OMe DMT-appropriate responding. It is concluded that certain of the substituted phenylisopropylamines, unlike amphetamine itself, can produce effects in rats similar to those produced by the training dose of 5-OMe DMT, and that a serotonergic mechanism might be involved.

Discriminative stimulus 5-OMe DMT Phenylisopropylamines Amphetamines Hallucinogens Serotonin

1. Introduction

Numerous phenylisopropylamines are psychoactive in man, and can produce effects which are amphetamine-like and/or LSD-like (Aldous et al., 1974; Martin et al., 1978 and references therein). Furthermore, unsubstituted racemic phenylisopropylamine (i.e. amphetamine, PIA) possesses a low affinity for the serotonin (5-HT) receptors of the isolated rat fundus preparation, while introduction of various substituent groups can enhance affinity by several hundred-fold (Glennon et al., 1980a). It has been proposed that substituted phenylisopropylamines represent a series of compounds whose activities vary on an amphetamine-like to serotonergic continuum, at least from an affinity standpoint. That is, even though all of the phenylisopropylamines bear a structural similarity to amphetamine, there is no reason to believe that all of these compounds act via the same mechanism in vivo. Those compounds which possess a high 5-HT receptor affinity might act primarily via a serotonergic mechanism whereas those with a low affinity might act via a mechanism (and produce in vivo effects) common to amphetamine. For example, the behavioral effects of amphetamine, but not its 2,5-dimethoxy-4-methyl derivative (i.e. DOM) can be blocked with the dopamine antagonist haloperidol, while the effects of DOM, but not amphetamine, can be blocked with 5-HT antagonists (Silverman and Ho, 1980).

The aim of this present investigation is to determine which of the various substituted phenylisopropylamines are capable of producing what might be considered as a 5-HT mediated response in animals. In this study, then, rats trained to discriminate 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT) from saline will be challenged with a series of phenylisopropylamine derivatives; generalization of the 5-OMe DMT cue to that produced by certain phenylisopropylamines might then be considered evidence for serotonergic involvement.

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2. Materials and methods

2.1. Subjects

The animals used in this study were sixteen 150-day-old male Sprague-Dawley 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

Standard operant chambers (Coulbourn Model E10-10), housed within light-attenuating outer chambers, were used. Each chamber contained 2 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 2 levers. All programming and recording of data was done by solid-state and electromechanical equipment located in the same room.

2.3. 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. On the V1-15s schedule, lever responses are reinforced on a variable time interval averaging one reinforcement every 15 sec. Lever-press training on V1-15s continued until rates of responding stabilized. At this point, drug discrimination training was begun.

Rats were injected intraperitoneally (i.p.) with either 5-OMe DMT (3.0 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 5-OMe DMT was administered on a double alternation schedule (i.e., 2 days saline —2 days 5-OMe DMT). 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 2.5-min extinction periods included total responses (expressed as responses/min) and percent responding on the 5-OMe DMT-appropriate lever (number of responses on 5-OMe DMT-designated lever/total number of responses). After 40 training sessions, discrimination performance was stable (i.e. 5-OMe DMT $\geq 85\%$, responses/min $= 12.8 \pm 3.2$; saline $\leq 12\%$, 13.3 ± 2.8 responses/min).

2.4. Substitution testing

Maintenance of the 5-OMe DMT-saline discrimination was insured by continuation of training sessions throughout substitution testing. Test data from animals not discriminating 5-OMe DMT (i.e. less than 80% correct responding when given drug) from saline ($> 20\%$ when given vehicle) during training prior to substitution test sessions were excluded; thus, a given test session may not have employed all 16 animals. 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 3, separated any 2 test sessions.

The first substitution tests investigated the dose-response and time-duration parameters of the 5-OMe DMT stimulus. Dose-response studies assessed the 5-OMe DMT-appropriate responding of the rats following the administration of 0.30, 0.75, 1.0, 1.5 and 3.0 mg/kg of the training drug. Doses were given to each animal in a random order. The time-duration parameter investigated the effects of increasing the time interval between the injection of the 5-OMe DMT training dose and the beginning of a test session. In addition to the standard 15 min delay, the effects of 30, 45, 60 and 120 min injection-time intervals were studied. Injection-time intervals were examined in a random order.

The next phase of substitution testing investi-

gated the ability of the 5-OMe DMT cue to generalize to the phenylisopropylamine compounds. Three to ten different increasing doses of challenge compound were administered to the animals. When a given dose resulted in 40–70% 5-OMe DMT-appropriate lever responding (partial generalization), the dose was increased by small increments until either generalization (≥ 75% 5-OMe DMT-appropriate responding) occurred or until disruption of behavior (total responses ≤ 5 during the extinction period) was observed. Each dose of each compound was administered to a group of three (usually) to six animals. When generalization occurred (table 1), and the number of animals in that particular group which received the dose which resulted in generalization, numbered less than four or five, an additional group of three different animals was run at the dose at which generalization occurred. The generalization dose (i.e. dose at which generalization occurred) thus reflects the average responding of a minimum of four animals (for R(−)-MDA and (±)-2,5-DMA), but otherwise reflects the responding of at least five animals. For those compounds where generalization occurred, ED_{50} values were determined from the dose-response data by the method of Litchfield and Wilcoxon (1949).

2.5. *Affinity determinations*

Using the isolated rat fundus preparation, dose response curves were obtained for 5-HT in the absence and in the presence of increasing concentration of test compound. We have previously described the methodology in greater detail (Glennon et al., 1980a). Receptor affinities are reported as pA_2 values, as calculated by the method of Arunlakshana and Schild (1959).

2.6. *Drugs*

All compounds used in this study were synthesized or obtained as previously reported (Glennon et al., 1980a) and were used as their hydrochloride salts. 2,5-Dimethoxy-3-methyl- and 2,5-dimethoxy-3-bromophenylisopropylamine were used as their oxalate salts, and 5-OMe DMT as the hydrogen oxalate salt. All solutions were prepared fresh daily in normal saline.

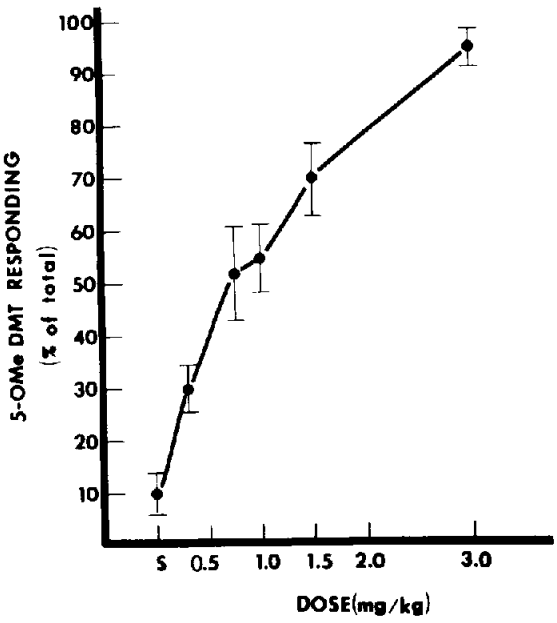


Fig. 1. Dose response curve for the administration of 5-OMe DMT to rats trained to discriminate 5-OMe DMT (3.0 mg/kg) from saline (S) (each point represents n = 16).

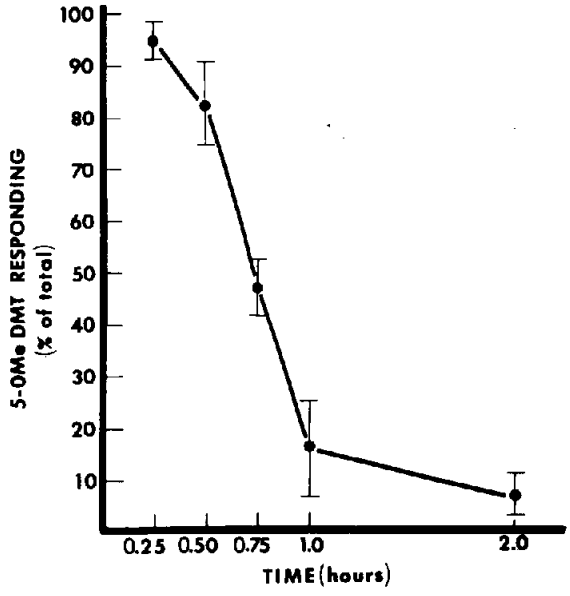


Fig. 2. Time-course of 5-OMe DMT (3.0 mg/kg) administered to 5-OMe DMT-trained animals (n = 13).

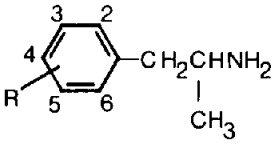
3. Results

Analysis of discrimination-responding, over the course of the study, revealed that the animals consistently responded 85–96% (7.4 to 11.4 responses/min) on the 5-OMe DMT-designated lever when given 5-OMe DMT, and 0–16% (6.9–13.7 responses/min) on the 5-OMe DMT-designated lever when given saline. This effect, for 5-OMe DMT, is dose-dependent (fig. 1); time-course studies reveal that after 15–30 min, percent 5-OMe DMT-appropriate responding decreases rapidly (fig. 2).

A total of thirty-six phenylisopropylamines (or optical isomers) were evaluated and the results are shown in tables 1–3. Based on the results of this study, the phenylisopropylamines can be conveniently divided into three categories. In the first category (Generalization), there are nine compounds which were found to produce a high degree of 5-OMe DMT-like responding, i.e. >75% responding on the 5-OMe DMT-appropriate lever (table 1). Response rate (5.1–11.3 responses/min) of animals administered these compounds, at the dose which produced generalization, was similar to that for 5-OMe DMT or saline. Increases in per-

TABLE 1

Data on compounds for which generalization occurred.



Compound	R_2	R_3	R_4	R_5	R_6	Dose-range evaluated, mg/kg	Number of doses
R(−)-DOM	OMe	H	Me	OMe	H	0.25–1.5	4
(±)-DOM	OMe	H	Me	OMe	H	0.25–1.5	4
R(−)-MDA	H	H	O-CH_2—O		H	0.50–1.5	3
(±)-MDA	H	H	O-CH_2—O		H	0.50–2.0	4
(±)-2-OMe-4,5-MDA	OMe	H	O-CH_2—O		H	1.0 –5.0	3
(±)-2,5-DMA	OMe	H	H	OMe	H	2.0 –5.0	4
(±)-2,4,6-TMA	OMe	H	OMe	H	OMe	1.0 –6.0	4
(±)-4-Me-2,6-DMA	OMe	H	Me	H	OMe	1.5 –3.5	3
(±)-6-Me-2,4-DMA	OMe	H	OMe	H	Me	1.0 –5.0	5

Compound	Number of determinations [a]	Maximal % responding [b]	ED_{50} [c] mg/kg	pA_2 [d]
R(−)-DOM	19 [h]	84 (±3.3)	0.38 (0.14–1.02)	7.15
(±)-DOM	19 [h]	82 (±1.9)	0.49 (0.22–1.11)	7.12
R(−)-MDA	10	88 (±3.1)	0.85 (0.38–1.94)	6.61
(±)-MDA	16	80 (±2.3)	1.05 (0.56–1.95)	6.45
(±)-2-OMe-4,5-MDA	15	95 (±1.6)	2.45 (1.09–4.75)	6.65
(±)-2,5-DMA	12	96 (±1.1)	2.42 (1.41–4.14)	6.83
(±)-2,4,6-TMA	15	80 (±2.0)	3.00 (1.3 –6.91)	6.28
(±)-4-Me-2,6-DMA	11	75 (±1.4) [e]	2.25 (1.09–4.66)	6.33 [f]
(±)-6-Me-2,4-DMA	21 [h]	81 (±3.5)	2.48 (1.03–5.98)	7.21 [g]

[a] Sum of the total number of doses × number of animals. [b] Maximal 5-OMe DMT-appropriate responding observed followed by ±S.E.M. [c] The ED_{50} value is followed by 95% confidence limits. [d] Unless otherwise noted, pA_2 values have been previously reported (Glennon et al., 1980a). [e] Insufficient compound to test at higher doses. [f] pA_2 values not previously reported; $pA_2 = 6.33$ (±0.22), slope of Schild plot $= -1.04$ (±0.27) for six determinations. [g] pA_2 value not previously reported; $pA_2 = 7.21$ (±0.12), Schild slope $= -0.95$ (±0.02) for three determinations. [h] Several animals used more than once.

TABLE 2

Data on compounds for which partial generalization occurred [a].

Compound	R_2	R_3	R_4	R_5	R_6	Dose-range evaluated, mg/kg	Number of doses
(±)-3-OMe-PIA	H	OMe	H	H	H	2.0 – 5.0	5
(±)-4-OMe-PIA	H	H	OMe	H	H	0.5 – 4.0	6
R(−)-4-OMe-PIA	H	H	OMe	H	H	0.5 – 2.0	5
(±)-2,3-DMA	OMe	OMe	H	H	H	3.0 – 8.0	5
(±)-3,4,5-TMA	H	OMe	OMe	OMe	H	0.75– 5.0	10
(±)-DOB	OMe	H	Br	OMe	H	0.5 – 1.5	6
(±)-3-Me-2,5-DMA	OMe	Me	H	OMe	H	1.0 –15.0	7

Compound	Total number of determinations	Highest nondisruption dose [b]	Maximal % responding [c]	pA_2 [d]
(±)-3-OMe-PIA	15	2.5	40 (± 11.6)	5.93
(±)-4-OMe-PIA	28 [e]	3.5	67 (± 9.8)	5.15
R(−)-4-OMe-PIA	15	1.75	60 (± 9.6)	5.38
(±)-2,3-DMA	19 [e]	7.5	60 (± 10.5)	5.54
(±)-3,4,5-TMA	35 [e]	1.85	60 (± 8.6)	5.60
(±)-DOB	26 [e]	1.35	54 (± 12.2)	7.35
(±)-3-Me-2,5-DMA	21 [e]	13.25	50 (± 14.3)	5.33

[a] Partial generalization (40–67% 5-OMe DMT-appropriate responding) was followed by disruption of behavior at the next highest dose(s) tested. [b] Highest dose (mg/kg) at which disruption was not observed; higher doses resulted in disruption. [c] Maximal 5-OMe DMT-appropriate responding observed. [d] pA_2 values have been previously reported (Glennon et al., 1980a). [e] Several animals used more than once.

cent 5-OMe DMT-appropriate responding were dose-related. In the second category (table 2) partial generalization (40–67% 5-OMe DMT-appropriate responding) was observed; attempts to increase the dose of challenge compound beyond that which gave maximal percent responding on the 5-OMe DMT-appropriate lever resulted in disruption of behavior (≤ 5 responses during the entire 2.5-min test session). Response rate of animals receiving drugs listed in table 2 was 3.0–7.2 responses/min at the test dose (table 2, column labeled Highest non-disruption dose) just prior to that which produced disruption of responding. In the final category (table 3) are compounds which elicited less than 40% 5-OMe DMT-appropriate responding; again, increasing the dose administered resulted in disruption of behavior. Response rate of animals receiving these agents ranged from 1.4 to 5.6 responses/min at the test dose prior to that which produced disruption. In addition to the above three categories, i.e. generalization, partial generalization, disruption, several compounds were found to produce saline-like responding at their highest dose tested; response rate, at the highest test dose, was in the range of 4.0 – 8.6 responses/min. The agents which fall into this category (followed by highest dose evaluated and maximum 5-OMe DMT-appropriate responding) include: 2,6-DMA (7 mg/kg, 37%), 3,5-DMA (7.0 mg/kg, 21%). 2,3,4-TMA (7.0 mg/kg, 21%) and 2,3,5-TMA (9.0 mg/kg, 36%). The pA_2 values determined for these four compounds are 5.09, 5.56, 5.07 and 5.38, respectively (Glennon et al., 1980a).

Cathinone, which is structurally related to the phenylisopropylamines, and which may be considered as β-keto amphetamine, was also evaluated. The 5-OMe DMT cue did not generalize to cathinone (table 3). Generalization does occur, however, when (±)-cathinone is administered to amphetamine-trained rats (unpublished observation).

Serotonin receptor affinity (pA_2) data have been previously determined for most of the phenyliso-

TABLE 3

Data on compounds for which disruption occurred [a].

Compound	R_2	R_3	R_4	R_5	R_6	Dose-range evaluated, mg/kg	Number of doses
S(+)-DOM	OMe	H	Me	OMe	H	1.0 – 5.0	4
(±)-DOEt	OMe	H	Et	OMe	H	0.1 – 1.5	5
R(−)-DOEt	OMe	H	Et	OMe	H	0.1 – 0.3	3
S(+)-DOEt	OMe	H	Et	OMe	H	0.5 – 1.0	3
(±)-PIA	H	H	H	H	H	0.5 – 3.0	4
(±)-2-OMe-PIA	OMe	H	H	H	H	2.0 – 5.0	4
S(+)-4-OMe-PIA	H	H	OMe	H	H	0.5 – 2.0	3
S(+)-MDA	H	H	O-CH_2	O	H	1.0 – 3.0	4
(±)2,4-DMA	OMe	H	OMe	H	H	1.0 – 7.0	5
(±)-3,4-DMA	H	OMe	OMe	H	H	0.5 – 1.0	3
(±)-2,4,5-TMA	OMe	H	OMe	OMe	H	0.5 – 5.0	10
(±)-2-OEt-4,5-DMA	OEt	H	OMe	OMe	H	2.0 – 7.0	3
(±)-4-OEt-2,5-DMA	OMe	H	OEt	OMe	H	2.0 – 7.0	4
(±)-5-OEt-2,4-DMA	OMe	H	OMe	OEt	H	2.0 – 7.0	3
(±)-3-Br-2,5-DMA	OMe	Br	H	OMe	H	3.0 –12.0	5
(±)-Cathinone						0.025– 4.8	10

Compound	Total number of determinations	Disruption dose [b] mg/kg	Maximal % responding [c]	pA_2
S(+)-DOM	20 [e]	5.0	35 (±14.8)	6.41
(±)-DOEt	18 [e]	0.75	22 (±11.7)	7.18
R(−)-DOEt	11	0.3	34 (±15.6)	–
S(+)-DOEt	9	1.0	20 (± 4.3)	–
(±)-PIA	19 [e]	3.0	21 (± 9.4)	5.27
(±)-2-OMe-PIA	12	3.5	20 (± 8.6)	5.54
S(+)-4-OMe-PIA	9	2.0	26 (±10.4)	5.16
S(+)-MDA	12	3.0	11 (± 3.6)	6.08
(±)-2,4-DMA	15	7.0	32 (±12.2)	5.60
(±)-3,4-DMA	9	1.0	14 (± 4.6)	5.45
(±)-2,4,5-TMA	36 [e]	3.0	32 (±10.9)	6.81
(±)-2-OEt-4,5-DMA	9	7.0	5 (± 3.2)	[d]
(±)-4-OEt-2,5-DMA	12	2.75	22 (±14.3)	–
(±)-5-OEt-2,4-DMA	12	7.0	20 (±12.9)	–
(±)-3-Br-2,5-DMA	19 [e]	10.5	21 (±15.8)	5.27
(±)-Cathinone	35 [e]	2.4	14 (± 1.9)	5.55

[a] Maximal 5-OMe DMT-appropriate responding never exceeded 35%. [b] Minimal dose at which disruption was observed. [c] Maximal 5-OMe DMT-appropriate responding observed prior to administration of the dose which produced disruption. [d] Valid pA_2 value could not be determined; Schild slopes = −0.60 to −0.70 suggesting interaction not of a competitive nature. [e] Some animals used more than once.

propylamines; these data are included in the tables. In several instances, pA_2 data were not available and were determined employing previously reported methodology. Although there is no significant correlation between pA_2 and ED_{50}, all of the compounds, for which generalization occurred, possess a $pA_2 > 6.25$.

4. Discussion

Phenylisopropylamines produce a variety of behavioral effects in both human and non-human species. These effects, depending on the presence and location of pendant substituent groups, can range from locomotor stimulation to, in man, hal-

lucinations. Several previous investigations have concluded that the effects produced by these compounds can be amphetamine-like and/or LSD-like (see Introduction). In animals, the behavioral effects of DOM, for example, can be attenuated by prior administration of 5-HT antagonists (Tilson et al., 1975; Winter, 1978; Silverman and Ho, 1980) but not by administration of a dopamine antagonist (Silverman and Ho, 1980). Thus, it might be assumed that the mechanism of action of DOM involves a serotonergic component. Further evidence, in this regard, is that other agents for which a 5-HT mechanism has been implicated have been demonstrated to generalize with the DOM stimulus in tests of discriminative responding (Tilson et al., 1975; Winter, 1978; Silverman and Ho, 1978). 5-OMe DMT can serve as a discriminative stimulus in animals when paired with saline; furthermore, the effects of 5-OMe DMT can be attenuated by pretreatment of animals with a 5-HT antagonist (Glennon et al., 1980b). Because DOM possesses a high affinity for 5-HT receptors and because generalization occurs when DOM is administered to 5-OMe DMT-trained animals (Glennon et al., 1980b), it was anticipated that the 5-OMe DMT cue might also generalize with other related phenylisopropylamines which also possess a relatively high affinity for 5-HT receptors. Indeed, generalization was found to occur with nine phenylisopropylamines (and/or isomers), each of which possesses a pA_2 value greater than 6.25. It might be inferred that these compounds are capable of producing interoceptive cues similar to those produced by the training dose of 5-OMe DMT. The 5-OMe DMT cue did not generalize with three-fourths of the compounds evaluated; of these 27 compounds, only four had pA_2 values of greater than 6.25 (it might be noted that the vast majority of the test compounds possess only alkoxy groups; in this last group of four compounds, three possess an alkyl or bromo group in addition to the alkoxy groups). The only simple methoxy compound which deviates from the data presented in table 1 is 2,4,5-trimethoxyphenylisopropylamine (2,4,5,-TMA); two different batches of this compound were evaluated and the data were consistent throughout.

The compounds in tables 2 and 3 apparently produce cues which differ from those produced by the training dose of 5-OMe DMT. These compounds (particularly those in table 3) may possess a mechanism of action which differs from that of 5-OMe DMT and the phenylisopropylamines in table 1. If a serotonergic component exists, it may be overshadowed by some other central effect(s).

As we have previously emphasized (Rosecrans and Glennon, 1979), generalization, in this paradigm, is not necessarily a predictor of hallucinogenic potential; nevertheless, many of the compounds to which the 5-OMe DMT cue generalizes are in fact hallucinogenic in man. Of those nine phenylisopropylamines in table 1, (i.e. where generalization occurred) all have pA_2 values greater than 6.25 and eight are known to be hallucinogenic in man (Shulgin, 1978); 6-Me-2,4-DMA, the last entry in table 1, has not been evaluated in humans. It might be concluded, then, that these phenylisopropylamines can produce effects similar to those of the training dose of 5-OMe DMT and that these effects appear to be mediated, at least in part, via a serotonergic mechanism. This is not to imply that other mechanism can not be involved, or even that these compounds do not produce amphetamine-like effects as a minor component of their overall spectrum of action. MDA, for example, has been reported to produce amphetamine-like effects while DOM appears to produce a dose-dependent biphasic response in man (Shulgin, 1978).

Of the remaining compounds, several have not been studied in man, most are relatively inactive, behaviorally, and only a few have been reported to be (weakly) 'psychotomimetic' in more than one human experiment. Of those few active compounds, their effects possess a considerable amphetamine-like stimulation component (Shulgin, 1978). Of notable exception are the hallucinogenic 2,4,5-TMA and 4-OEt-2,5-DMA, for which no explanation can be offered at this time.

The results of this study suggest that the class of compounds referred to as phenylisopropylamines may actually consist of several behavioral sub-classes. The compounds in table 1 may, like 5-OMe DMT, possess more of a serotonergic component to their mechanism of action than the remainder of the phenylisopropylamines evaluated.

Furthermore, this serotonergic mechanism may differ from that for the mono-methoxyphenylisopropylamines which apparently enhance release of 5-HT (Menon et al., 1976; Tseng et al., 1976; Tseng, 1978). For the most part, there is excellent agreement between those phenylisopropylamines which may be considered hallucinogenic or DOM-like and the generalization data obtained in this investigation. In addition, those compounds which are the most active in man, possess high 5-HT receptor affinities and, with the exception of compounds such as DOEt and DOB (which may produce effects in man which are qualitatively dissimilar to those of DOM) and 2,4,5-TMA, they apparently produce effects in rats similar to those produced by the hallucinogen 5-OMe DMT.

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