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The Paradox of 5-Methoxy-*N,N*-Dimethyltryptamine: An Indoleamine Hallucinogen That Induces Stimulus Control Via 5-HT_{1A} Receptors

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WINTER, J. C., R. A. FILIPINK, D. TIMINERI, S. E. HELSLEY AND R. A. RABIN. *The paradox of 5-methoxy*-N,N-*dimethyltryptamine: An indoleamine hallucinogen that induces stimulus control via 5-HT_{1A} receptors*. PHARMACOL BIOCHEM BEHAV **65**(1) 75–82, 2000.—Stimulus control was established in rats trained to discriminate either 5-methoxy-*N,N*-dimethyltryptamine (3 mg/kg) or (−)-2,5-dimethoxy-4-methylamphetamine (0.56 mg/kg) from saline. Tests of antagonism of stimulus control were conducted using the 5-HT_{1A} antagonists (±)-pindolol and WAY-100635, and the 5-HT_2 receptor antagonist pirenperone. In rats trained with 5-MeO-DMT, pindolol and WAY-100635 both produced a significant degree of antagonism of stimulus control, but pirenperone was much less effective. Likewise, the full generalization of 5-MeO-DMT to the selective 5-HT_{1A} agonist [±]-8-hydroxy-dipropylaminotetralin was blocked by WAY-100635, but unaffected by pirenperone. In contrast, the partial generalization of 5-MeO-DMT to the 5-HT_2 agonist DOM was completely antagonized by pirenperone, but was unaffected by WAY-100635. Similarly, in rats trained with (−)-DOM, pirenperone completely blocked stimulus control, but WAY-100635 was inactive. The results obtained in rats trained with (−)-DOM and tested with 5-MeO-DMT were more complex. Although the intraperitoneal route had been used for both training drugs, a significant degree of generalization of (−)-DOM to 5-MeO-DMT was seen only when the latter drug was administered subcutaneously. Furthermore, when the previously effective dose of pirenperone was given in combination with 5-MeO-DMT (SC), complete suppression of responding resulted. However, the combination of pirenperone and WAY-100635 given prior to 5-MeO-DMT restored responding in (−)-DOM-trained rats, and provided evidence of antagonism of the partial substitution of 5-MeO-DMT for (−)-DOM. The present data indicate that 5-MeO-DMT–induced stimulus control is mediated primarily by interactions with 5-HT_{1A} receptors. In addition, however, the present findings suggest that 5-MeO-DMT induces a compound stimulus that includes an element mediated by interactions with a 5-HT_2 receptors. The latter component is not essential for 5-MeO-DMT–induced stimulus control, but is revealed in animals tested or trained with a 5-HT_2-selective agonist such as (−)-DOM. Based upon the present data, we conclude that 5-MeO-DMT differs from DOM with respect to the serotonergic element that mediates stimulus control in the rat, but that it shares with DOM a functionally significant interaction with 5-HT_2 receptors. © 1999 Elsevier Science Inc.

5-Methoxy-*N,N*-dimethyltryptamine Drug-induced stimulus control 5-HT_{1A} 5-HT_{2A} Rat

FOLLOWING the demonstration that hallucinogens can function as discriminative stimuli in animals (22), drug-induced stimulus control has often been used in attempts to establish the mechanism of action of these agents. Thus, for example, the observation that the stimulus effects of mescaline—a phenethylamine hallucinogen—are blocked by serotonergic antagonists (6,43) provided support for the venerable hypothesis of Gaddum (12) that receptors for 5-hydroxytryptamine (5-HT) are crucial to the action of hallucinogenic drugs. This observation was later extended to other hallucino-

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gens including lysergic acid diethylamide [LSD; (27,44)], 2,5-dimethoxy-4-methylamphetamine [DOM; (44)], and *N,N*-dimethyltryptamine [DMT; (16)]. Although serotonergic systems are clearly relevant to the effects of LSD, the question remains as to which specific 5-HT receptor subtypes are involved. This issue has become more complicated as the original division of 5-HT receptors into 5-HT_1 and 5-HT_2 subtypes (33) has been expanded and reorganized to include seven distinct families or classes of 5-HT receptors, with some families including multiple subtypes (23).

The observed blockade of the stimulus effects of DOM, LSD, and mescaline by 5-HT antagonists that were considered relatively selective for the 5-HT_2 receptor subtype led Glennon and colleagues to hypothesize that classical hallucinogens act as 5-HT_2 agonists (14,17,18,30). Subsequently, the close correlation between affinities of the 5-HT_{2A} and 5-HT_{2C} receptor subtypes for serotonergic ligands suggested that the 5-HT_{2C} receptor may play an independent or complementary role in hallucinogenic activity (34,41). However, using a series of nonselective serotonergic antagonists, it was concluded on the basis of antagonist correlation analysis that the 5-HT_{2A} receptor exerts a predominant influence in the stimulus effects of indoleamine and phenethylamine hallucinogens (9). Using purportedly selective 5-HT_{2A} and 5-HT_{2C} antagonists, Schreiber et al. (35) had earlier reached the same conclusion with respect to the stimulus effects of 2,4-dimethoxy-4-iodoamphetamine.

Against this background, stimulus control by the indoleamine hallucinogen, 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), is puzzling. In the most extensive analysis to date of 5-MeO-DMT–induced stimulus control, Spencer and colleagues (38) concluded that "the 5-HT_{1A} receptor subtype is strongly involved. . ." Although it is true that a number of investigators have suggested that 5-HT_{1A}–mediated events are factors in the behavioral effects of phenethylamine and indoleamine hallucinogens (1,5,19,32,41), this receptor appears to play a modulatory role rather than be directly involved in the stimulus effects of the hallucinogens. With respect to 5-MeO-DMT, the conclusion reached by Spencer et al. (38) was based primarily upon (a) the fact that the potencies of drugs substituting for 5-MeO-DMT were best correlated with affinities at the 5-HT_{1A} receptor; and (b) a significant degree of blockade by pindolol, a drug which, when beta-adrenergic systems can be ruled out, functions as a selective antagonist at the 5-HT_{1A} receptor (42). In addition, binding data show high affinity of 5-MeO-DMT for 5-HT_{1A} receptors (20,38), and behaviorally significant activity at those receptors is indicated by similar effects of 8-OH-DPAT and 5-MeO-DMT on forepaw treading in the rat (42) and by the complete generalization of TVX Q 7821, a highly selective 5-HT_{1A} agonist, to 5-MeO-DMT (37).

The present investigation was designed to test the hypothesis that stimulus control by 5-MeO-DMT is mediated by 5-HT_{1A} receptors. In addition, the hypothesis that 5-MeO-DMT produces functionally significant effects at 5-HT_{2A} receptors was tested using the antagonists, WAY-100635, and pirenperone, in rats trained with 5-MeO-DMT and with (−)-DOM.

METHOD

Animals

Male Fischer-344 rats were obtained from Charles River Breeding Laboratories, Inc. (Wilmington, MA) at an age of approximately 6 weeks. They were housed in pairs, and allowed free access to water in the home cage. All handling and testing occurred during daytime hours. Standard rat chow was provided immediately following training sessions. Caloric intake was controlled so as to maintain adult body weights of approximately 300 g. All animals used were maintained in accordance with the *Guide for Care and Use of Laboratory Animals* of the Institute of Laboratory Animal Resources, National Research Council. All experimental protocols were approved by the Laboratory Animal Care Committee of SUNY at Buffalo.

Apparatus

Six small-animal test chambers (Coulbourne Instruments model E 10-10) were used for all experiments. These were housed in larger light-proof, sound-insulated boxes that contained a house light and an exhaust fan. Chambers contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper that delivered 0.1 ml of sweetened condensed milk diluted 2:1 with tap water. Sessions were managed by a micro-computer using operant control software (Coulbourne Instruments D91-12, version 4.0).

Procedure

Training. After learning to drink from the dipper, rats were trained to press first one and then the other of the two levers. The number of responses for each reinforcement was gradually increased from 1 to 10. During this time, the reinforced lever was alternated on a random basis. All subsequent training and testing sessions used a fixed-ratio 10 (FR10) schedule of reinforcement. Discrimination training was then begun. Before each 10 min training session, subjects were injected IP with either saline or drug. Following the administration of drug, every tenth response on the drug-appropriate lever was reinforced. Similarly, responses on the saline-appropriate lever were reinforced on a FR10 schedule following the injection of saline. For half of the subjects, the left lever was designated as the drug-appropriate lever. During discrimination training, drug, and saline were alternated on a daily basis. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, 83% or more of all responses prior to the delivery of the first reinforcer were on the appropriate lever.

Groups of animals were trained with 5-MeO-DMT (n = 12) or (−)-DOM (n = 9). Pretreatment times for the IP injection of 5-MeO-DMT (3 mg/kg) and (−)-DOM (0.56 mg/kg) were 15 (15) and 75 (8) min, respectively. After stimulus control with the training drugs was well established, tests of generalization and of antagonism were conducted once per week in each animal as long as performance during the remainder of the week did not fall below a criterion level of 83% correct responding. Subjects were assigned to test groups with the intention of including equal numbers of those trained on the previous day with saline and drug, respectively. During test sessions, no responses were reinforced, and the session was terminated after the emission of 10 responses on either lever. The distribution of responses between the two levers was expressed as the percentage of total responses emitted on the drug-appropriate lever. Response rate was calculated for each session by dividing total number of responses emitted prior to lever selection, that is, prior to the emission of 10 responses on either lever, by elapsed time.

For purposes of discussion of these data, complete generalization of a training drug to a test drug is said to be present when (a) a mean of 80% or more of all test responses occurs on the drug-appropriate lever; (b) there is no significant difference between the response distributions of the training

drug and the test drug; and (c) there is a statistically significant difference between the response distributions of the test drug and saline control sessions. An intermediate degree of generalization is defined as being present when response distributions after a test drug are less than 80% drug-appropriate, and are significantly different from both training conditions. Finally, when the response distribution after a test drug is not different from that in saline control sessions, an absence of generalization of the training drug to the test drug is assumed. Similar criteria are applied to the definitions of full, partial, and no antagonism. Thus, full antagonism is assumed to be present when (a) less than 20% of all test responses are on the training drug-appropriate lever; (b) there is no significant difference between the response distributions in the test of antagonism and the saline control, and (c) there is a statistically significant difference between the response distributions of the test drug alone and in combination with the antagonist.

Drugs

(±)-Pindolol, (±)8-hydroxy-dipropylaminotetralin HCl (8-OH-DPAT), and 5-methoxy-*N,N*-dimethyltryptamine oxalate were purchased from Research Biochemicals International. The following drugs were generously provided by the organizations indicated: (−)-DOM HCl (National Institute on Drug Abuse, Rockville, MD), WAY-100635 (Wyeth-Ayerst Research, Princeton, NJ), pirenperone (Janssen Pharmaceutica, Beerse, Belgium). All drugs were dissolved in 0.9% saline solution and injected in a volume of 1 ml/kg body weight. The IP route was employed for all drugs with the exception of WAY-100635, which was injected SC.

Statistical Analysis

Behavioral data expressed as "percent drug-appropriate responding" were transformed by squaring each value. If the transformed data passed tests of normality and equal variance, statistical significance was assessed using Student's *t*-test or analysis of variance with subsequent multiple comparisons by the method of Student–Newman–Keuls. In those instances when the transformed data failed either a test of normality or a test of equal variance, the Mann–Whitney rank-sum test or analysis of variance on ranks was used. Differences were considered to be statistically significant if the probability of their having arisen by chance was <0.05. All analyses were conducted using SigmaStat for Windows™ (Jandel Scientific Software, San Rafael, CA). In those instances when more than one drug was tested in combination with a training drug, control data were repeated for each comparison, and statistical analyses were applied using the appropriate control sessions. However, for purposes of clarity, mean values for control data are shown in all figures.

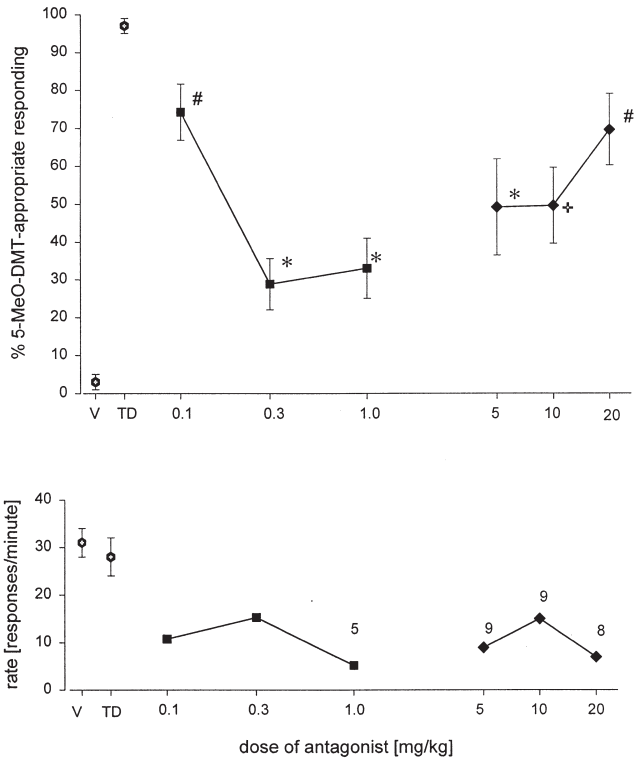

FIG. 1. Dose–response relationships for WAY-100635 (squares) and (±)-pindolol (diamonds) as antagonists of the training dose of 5-MeO-DMT (3 mg/kg). 5-MeO-DMT and (±)-pindolol were injected IP, 15 and 60 min, respectively, before testing. WAY-100635 was injected SC, 30 min before testing. Each point represents the mean of 1 determination in each of 10 subjects (±SEM). A number next to a data point on the rate panel indicates the number of subjects completing the session if less than 10. Ordinate: upper panel—mean percentage of responses on the 5-MeO-DMT–appropriate lever; lower panel—response rate. Data shown at points V and TD on the abscissa (open hexagons) are means (±SEM) for the vehicle (saline) and training drug sessions. Abscissa: dose plotted on a log scale. Statistical comparisons are between saline control, 5-MeO-DMT control, and the combination of antagonist and 5-MeO-DMT. *Significantly different ($p < 0.05$) from 5-MeO-DMT. #Significantly different from saline. +Significantly different from both 5-MeO-DMT and saline.

RESULTS

Figure 1 shows the effects of pretreatment with either WAY-100635 or pindolol on drug-appropriate responding following administration of the training dose of 5-MeO-DMT. Although neither drug blocked 5-MeO-DMT completely, both produced a significant intermediate degree of antagonism. In this regard, WAY-100635 was somewhat more effective and, given its greater selectivity for the 5-HT$_{1A}$ compared with pindolol (10,42), subsequent experiments employed WAY-100635.

The dose–response relationship for 5-MeO-DMT and the effects of the antagonists WAY-100635 and pirenperone are shown in Fig. 2A. At the two higher doses of 5-MeO-DMT, against which the antagonists were examined, WAY-100635 was clearly the more effective drug. Nonetheless, by the criteria applied in this study, pirenperone produced an intermediate degree of antagonism when given in combination with the training dose of 5-MeO-DMT.

When the prototypical 5-HT$_{1A}$ agonist, 8-OH-DPAT, was tested in rats trained with 5-MeO-DMT (Fig. 2A), complete generalization of the training drug was observed. However, the stimulus effects of 8-OH-DPAT were differentially blocked by pirenperone and WAY-100635. Although the former had no effect, WAY-100635 completely antagonized the substitution of 8-OH-DPAT for 5-MeO-DMT. With respect to the rate of responding, WAY-100635 antagonized the rate-suppressant effects of 8-OH-DPAT at a dose of 0.4 mg/kg. In contrast, pirenperone further suppressed responding in combination with the 0.6 mg/kg dose 8-OH-DPAT.

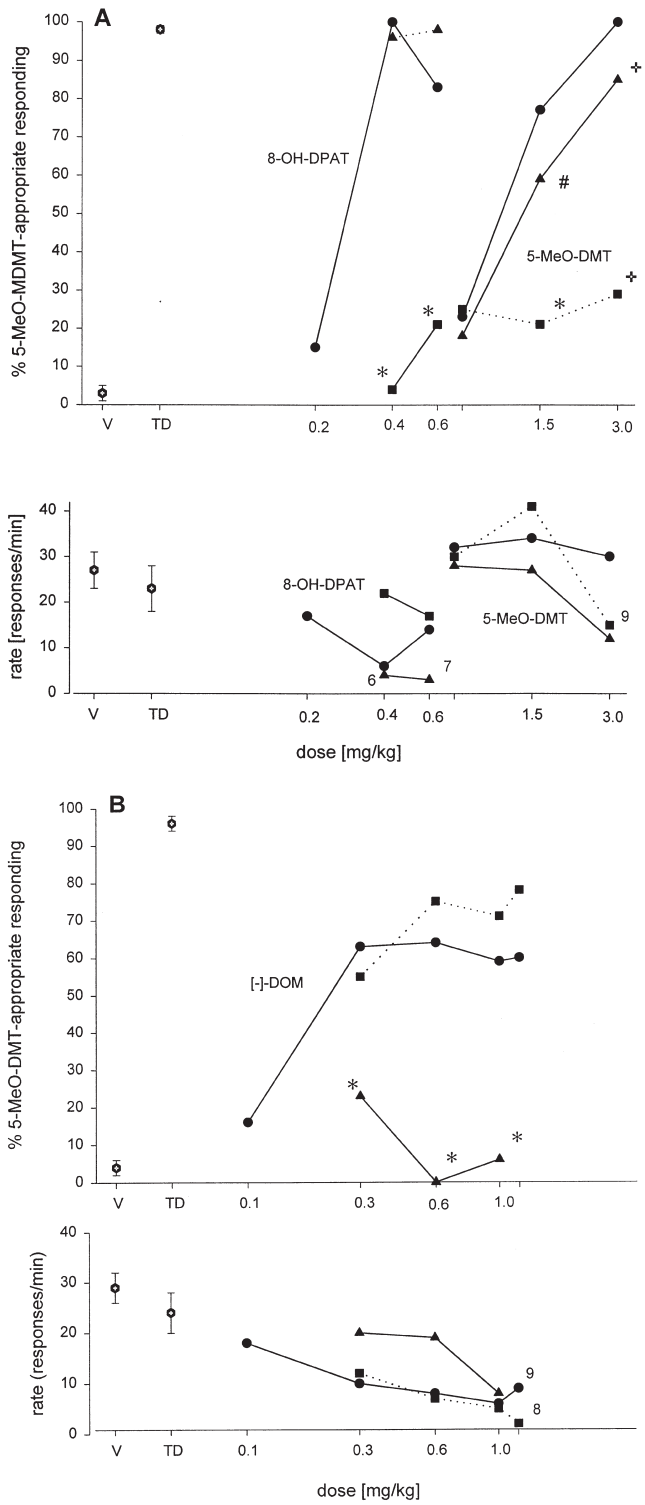

FIG. 2. (A) Dose–response relationships for 8-OH-DPAT and 5-MeO-DMT (circles) in rats trained with 5-MeO-DMT (3 mg/kg) as a discriminative stimulus and the interaction of 8-OH-DPAT and 5-MeO-DMT with pirenperone (0.16 mg/kg; triangles) and with WAY-100635 (0.3 mg/kg; squares). Pirenperone was injected IP, 60 min before testing. The points at 1.5 and 3.0 mg/kg of 5-MeO-DMT represent the mean of two determinations in each of the subjects. Statistical comparisons are between 8-OH-DPAT and 5-MeO-DMT, respectively, alone and in combination with either pirenperone or WAY-100635. All other details are as in Fig. 1. (B) Dose–response relationship for (−)-DOM (circles) in rats trained with 5-MeO-DMT (3 mg/kg) as a discriminative stimulus and the interaction of (−)-DOM with pirenperone (0.16 mg/kg; triangles) and with WAY-100635 (0.3 mg/kg; squares). Each point on the dose–response curve for 5-MeO-DMT represents the mean of three determinations in each subject. (−)-DOM was administered IP 75 min before testing. All other details are as in Fig. 1.

Figure 2B shows the tests of generalization of 5-MeO-DMT to the 5-HT_2-selective agonist, DOM. An intermediate degree of generalization was observed at all but the lowest dose tested. In addition, the results of tests in which DOM was combined with WAY-100635 and pirenperone, respectively, are shown. In contrast with the data presented in Fig. 2A for 5-MeO-DMT in rats trained with 5-MeO-DMT, the partial generalization of 5-MeO-DMT to (−)-DOM was completely blocked by pirenperone, while WAY-100635 was without antagonistic effects.

The dose–response relationship for (−)-DOM in rats trained with that drug (0.56 mg/kg) is shown in Fig. 3A, together with the interactions of (−)-DOM with the antagonists, WAY-100635, pindolol, and pirenperone. The results are as would be predicted from previous studies in that the 5-HT_{1A} antagonists, WAY-100635 and pindolol, were ineffective, while pirenperone produced complete antagonism. When 8-OH-DPAT was tested in (−)-DOM–trained subjects (data not shown), no generalization was observed, but WAY-100635 significantly antagonized the rate suppressant effects of 8-OH-DPAT.

When animals trained with (−)-DOM were tested with 5-MeO-DMT (Fig. 3A), no statistically significant generalization occurred at any dose. Furthermore, no significant interactions occurred between either pirenperone or WAY-100635 at doses of 5-MeO-DMT ranging from 0.3 to 3 mg/kg. However, at the highest dose tested (6 mg/kg), the combination of 5-MeO-DMT and WAY-100635 resulted in an intermediate degree of substitution for DOM. When the same (−)-DOM-trained rats were tested with 5-MeO-DMT administered via the subcutaneous route (Fig. 3B), a significant intermediate degree of generalization was observed together with a dose-related suppression of response rate. Although WAY-100635 did not block the partial substitution of 5-MeO-DMT for (−)-DOM, the suppression of response rates was significantly antagonized. When pirenperone was given in combination with 5-MeO-DMT, responding was completely suppressed; hence, stimulus control could not be assessed. However, the administration of both WAY-100635 and pirenperone in combination with 5-MeO-DMT resulted in a restoration of responding and a significant antagonism of the partial substitution of 5-MeO-DMT for (−)-DOM.

DISCUSSION

The data of Fig. 1 indicate a substantial degree of antagonism of 5-MeO-DMT–induced stimulus control both by WAY-100635 and by pindolol. The latter observation is in agreement with the results of Spencer et al. (38), although those investigators observed a somewhat higher degree of antagonism. We are unaware of any previous reports of the antagonism by WAY-100635 of stimulus control by 5-MeO-DMT but, given the high degree of selectivity of WAY-

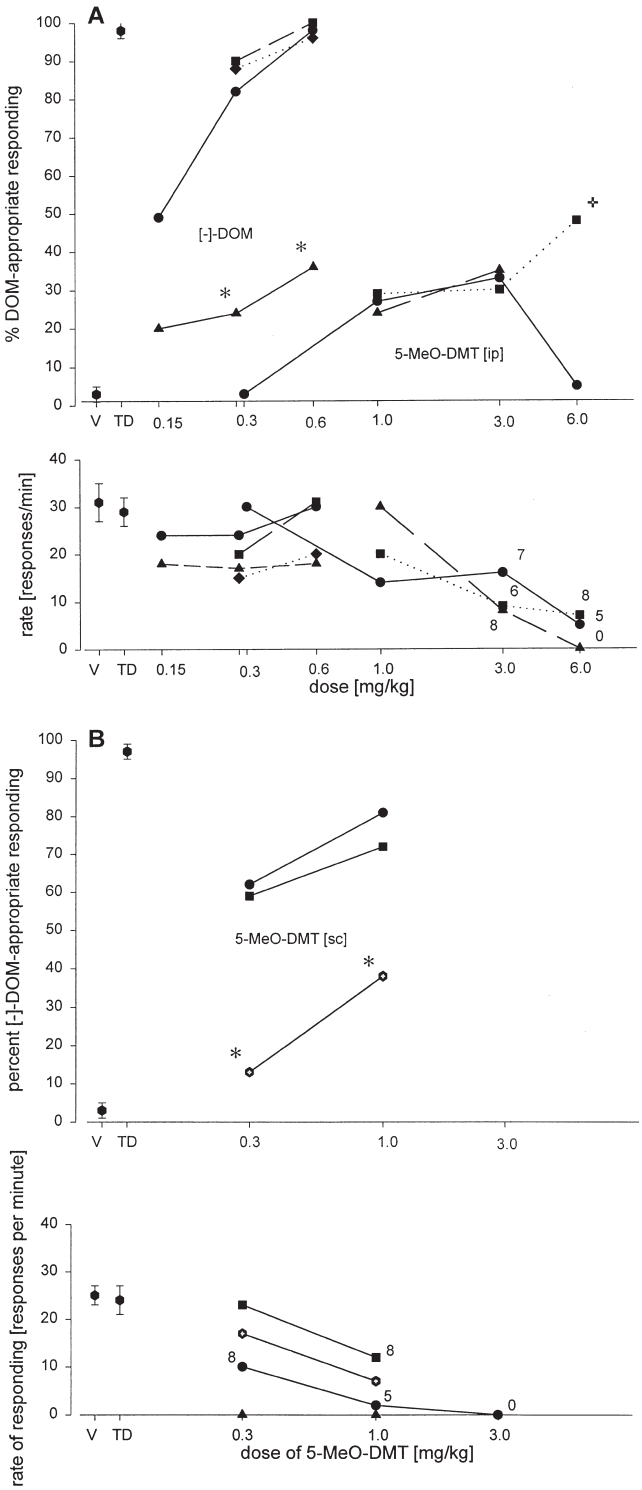

FIG. 3. (A) Dose–response relationships for (−)-DOM and 5-MeO-DMT (circles) in rats trained with (−)-DOM (0.56 mg/kg) as a discriminative stimulus and the interaction of (−)-DOM and 5-MeO-DMT with pirenperone (0.16 mg/kg; triangles), with WAY-100635 (0.3 mg/kg; squares), and with (±)-pindolol (5 mg/kg; diamonds). Each point represents the mean of one determination in each of nine subjects. A number next to a data point on the rate panel indicates the number of subjects completing the session if less than 9. *Significantly different from DOM alone. $^{+}$Significantly different from both training conditions. Data shown at points V and TD on the abscissa (closed hexagons) are means (±SEM) for the vehicle and training drug sessions. (B) Dose–response relationship for 5-MeO-DMT (circles) administered SC to rats trained with (−)-DOM as a discriminative stimulus and the interaction of 5-MeO-DMT with pirenperone (0.16 mg/kg; triangles), WAY-100635 (0.3 mg/kg; squares), and the combination of pirenperone and WAY-100635 (hexagons). *Significantly different from 5-MeO-DMT alone.

100635 for the 5-HT$_{1A}$ receptor (10), the data of Fig. 1 strongly support an effect mediated by that receptor.

The contrast seen in Fig. 2A between the respective abilities of WAY-100635 and pirenperone to antagonize the 5-MeO-DMT cue provides further evidence favoring the hypothesis that a 5-HT$_{1A}$-mediated mechanism predominates. Furthermore, these data argue that 5-MeO-DMT does not induce stimulus control via 5-HT$_{2A}$ receptors as do other indoleamine and phenethylamine hallucinogens (9,35). Although it is true that pirenperone is nonselective with respect to dopaminergic, adrenergic, and serotonergic receptors (26), it is more selective within the family of serotonergic receptors. Thus, in rat cortex, pirenperone exhibits an affinity for undifferentiated 5-HT$_2$ receptors, which is more than a thousand times greater than at the 5-HT$_{1A}$ receptor (24). Furthermore, previous studies have provided ample evidence that pirenperone is an effective antagonist of the stimulus effects of LSD-induced stimulus control and of the generalization of LSD to (±)-DOM (7,47) as well as of (−)-DOM–induced stimulus control [(9); present investigation, Fig. 3A]. Although it was earlier reported that pizotifen (pizotyline, BC-105), a drug that is moderately selective for 5-HT$_2$ receptors relative to 5-HT$_1$ receptors (28,47), completely antagonizes stimulus control by 5-MeO-DMT (15,49,50) when a training dose of 1.5 mg/kg is used, only partial blockade was observed by Spencer et al. (38) using a training dose of 1.25 mg/kg.

In the landmark study by Spencer et al. (38), complete generalization of 5-MeO-DMT to the 5-HT$_{1A}$-selective agonist, 8-OH-DPAT, was observed. That finding is fully replicated in Fig. 2A, together with a demonstration of complete antagonism of 8-OH-DPAT by the selective 5-HT$_{1A}$ antagonist, WAY-100635, and an absence of antagonism by pirenperone. It should be noted that generalization between 5-MeO-DMT and 8-OH-DPAT is not symmetrical in that animals trained with 8-OH-DPAT yielded a maximum of 38% 8-OH-DPAT–appropriate responding when tested with a range of doses of 5-MeO-DMT (13). However, Fozard et al. (11) made the interesting observation that full generalization occurred if the rats were pretreated with ketanserin prior to administration of 5-MeO-DMT. The authors interpreted this to suggest, in consonance with the present hypothesis, that 5-MeO-DMT produces functionally significant agonistic effects at both 5-HT$_{1A}$ and 5-HT$_2$ receptors, with the latter masking the former in 8-OH-DPAT–trained animals.

When (−)-DOM was tested in rats trained with 5-MeO-DMT, a significant intermediate degree of generalization was seen (Fig. 2B). This finding differs somewhat from the full generalization of 5-MeO-DMT to racemic DOM reported earlier by Glennon et al. (15). Of greater significance, however, is the contrast between the effects of WAY-100635 and pirenperone on stimulus control directly mediated by 5-MeO-DMT (Fig. 2A) and the effects of the antagonists upon the partial generalization of 5-MeO-DMT to (−)-DOM (Fig.

2B). In the former instance, the results are in keeping with 5-HT_{1A}-mediated interactions whereas, in the latter, 5-HT_2 receptors appear to predominate.

Turning now to rats trained with (−)-DOM, we see in Fig. 3A that pirenperone blocks stimulus control while doses of (±)-pindolol and WAY-100635, which were effective against 5-MeO-DMT (Fig. 1), are ineffective vs. (−)-DOM. These results are completely in keeping with the high degree of selectivity which (−)-DOM has for 5-HT_2 receptors (29) and with a previous demonstration of the antagonism of DOM-induced stimulus control by pirenperone (9,18). In view of the fact that complete generalization of (±)-DOM to 5-MeO-DMT had previously been reported (48), the absence of significant generalization seen in Fig. 3A is puzzling. Procedural differences between the present study and that of Young et al. (48), which might have contributed to this difference include (a) the use of (−)-DOM rather than the racemic mixture, (b) a pretreatment time for (−)-DOM of 75 min (14) instead of 15 min, (c) the use of a fixed-ratio 10 schedule of reinforcement rather than a VI 15-s schedule, and (d) termination of tests after the initial lever selection instead of after a 2.5-min test in extinction. Nonetheless, it is interesting that an intermediate degree of generalization was seen following the combination of a high dose of 5-MeO-DMT (6 mg/kg) in combination with WAY-100635. A plausible explanation of this finding is that by antagonizing the activity of 5-MeO-DMT at 5-HT_{1A} receptors, activity at 5-HT_2 receptors could be revealed. However, this explanation is not completely satisfying in that generalization remained less than complete, and the interaction was seen at only one dose of 5-MeO-DMT.

When 5-MeO-DMT was administered via the subcutaneous route to avoid the first pass effect, significant partial substitution for (−)-DOM was observed (Fig. 3B). Although pretreatment with WAY-100635 had no effect upon the generalization, significant antagonism of the rate-suppressant effects of 5-MeO-DMT was observed. The combination of pirenperone with 5-MeO-DMT led to complete suppression of responding. When 5-MeO-DMT was preceded by both pirenperone and WAY-100635, responding was restored to a level where stimulus control could be assessed and antagonism of the partial generalization of (−)-DOM to 5-MeO-DMT was seen. The basis for the rate-suppressing interaction between pirenperone and 5-MeO-DMT is unknown, but a similar effect was previously reported in rats trained with LSD (47). Viewed as a whole, the data of Fig. 3B are compatible with the present hypothesis that the compound stimulus induced by 5-MeO-DMT includes an element mediated by 5-HT_2 receptors.

Although many drugs are reputed to be highly selective in their actions, experience has shown that nearly all interact with multiple receptor types and subtypes, especially when a range of doses is examined. Thus, it is plausible to assume that a drug that is able to induce stimulus control may do so via a compound stimulus (40) in which the respective elements arise from discrete drug-receptor interaction (9). This formulation has been explored most fully by Ator and Griffiths (2–4), comparing stimulus control and generalization with benzodiazepines and barbiturates, drugs that share many properties but that are therapeutically and mechanistically differentiable. The Ator hypothesis explains asymmetric generalizations in terms of differential salience of the elements of a compound stimulus, depending upon which elements have been trained, and postulates that a nonselective drug may substitute for more specific agents but not vice versa. Adding to the complexity of these issues is the possibility that stimulus elements may not only act independently, but may also interact [e.g., (1,39)].

Crucial to the testing of the Ator hypothesis is the concept of what have been called intermediate results or partial generalizations (2,45). We are inclined to agree with Ator (2) that "the most parsimonious interpretation of intermediate responding across the range of doses of a drug other than the training drug would be that the test drug stimulus is both like and unlike the training drug stimulus. . ." After the presence of intermediate results is confirmed by adequate statistical analysis, selective pharmacological antagonists provide a powerful tool for their interpretation. Thus, for example, the fact that pirenperone blocks both DOM (Fig. 3A) and the partial substitution of DOM for 5-MEO-DMT (Fig. 2B) but is inactive (Fig. 2A) in rats trained with 5-MeO-DMT is most parsimoniously explained by a 5-HT_2-mediated element in the compound stimulus induced by 5-MeO-DMT. This element is not essential for the establishment of stimulus control by 5-MeO-DMT, but is revealed in subjects trained with a drug such as DOM, which acts primarily via 5-HT_2 receptors. Precedent for the present data and its interpretation is found in the study of 5-MeO-DMT by Spencer et al. (38), who observed that pizotyline completely blocked the substitution of quipazine for 5-MeO-DMT but was only partially active against 5-MeO-DMT itself; the authors were led to suggest the presence of an element mediated by 5-HT_2 receptors. Similar results have been seen with other serotonergic drugs. For example, the partial generalization of LSD to *p*-methoxyamphetamine is antagonized by pizotyline but PMA-induced stimulus control is unaffected by pizotyline (46). Similarly, pizotyline does not antagonize ibogaine-induced stimulus control, but does block the partial substitution of ibogaine in both LSD and (±)-DOM–trained rats (31). Finally, Helsley et al. (21) concluded the presence of a nonessential 5-HT_2-mediated element in stimulus control by ibogaine on the basis of the observation that pirenperone does not antagonize ibogaine-trained rats but the partial substitution of LSD and (−)-DOM for ibogaine is blocked; biochemical support for the presence of a 5-HT_2 component of ibogaine's actions was provided by the ability of ibogaine to protect 5-HT_2 receptors against alkylation by EEDQ.

In summary, the present data are compatible with the hypothesis that the indoleamine hallucinogen, 5-MeO-DMT, establishes stimulus control via actions at 5-HT_{1A} receptors. This conclusion is entirely in keeping with that drawn in an earlier study by Spencer et al. (38), and is further solidified by the use of the selective 5-HT_{1A} antagonist, WAY-100635, a drug not previously applied to the analysis of 5-MeO-DMT–induced stimulus control. However, the present data indicate as well that 5-MeO-DMT induces a compound stimulus that includes an element mediated by 5-HT_2 receptors. As predicted by the Ator hypothesis, the latter element is revealed in subjects trained with an agonist such as (−)-DOM, which acts predominantly at 5-HT_2 receptors. Because of the well-established views that indoleamine and phenethylamine hallucinogens such as LSD and DOM establish stimulus control in rats via agonist actions at 5-HT_2 receptors (9,14,35) and that human hallucinogenic activity likewise arises at those receptors (25), 5-HT_{1A}-mediated stimulus control by 5-MeO-DMT presents a paradox. Indeed, Strassman et al. (39) have suggested that the dimethyltryptamines may be unique among classic hallucinogens. Based upon the present data, we suggest as an alternative that 5-MeO-DMT differs from LSD and DOM with respect to the serotonergic element that mediates stimulus control in the rat, but that it shares with those drugs a

functionally significant interaction with 5-HT_2 receptors. While the present report was under editorial review, Smith et al. (36) published findings that are consonant with the present conclusions. Specifically, they demonstrated agonist properties for *N,N*-dimethyltryptamine, a closely related analog of 5-MeO-DMT, at 5-HT_{2A} and 5-HT_{2C} receptors in transfected fibroblasts as well as at endogenous 5-HT_{2C} receptors in rat choroid plexus.

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