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Serotonergic Receptor Subtypes and Hallucinogen-Induced Stimulus Control

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WINTER, J. C., D. J. FIORELLA, D. M. TIMINERI, R. A. FILIPINK, S. E. HELSLEY AND R. A. RABIN. *Serotonergic receptor subtypes and hallucinogen-induced stimulus control.* PHARMACOL BIOCHEM BEHAV **64**(2) 283–293, 1999.—More than a quarter century has passed since the demonstration that indoleamine and phenethylamine hallucinogens can function as discriminative stimuli in the rat, and that serotonergic systems are critically involved. During that period our knowledge of the physiology, pharmacology, biochemistry, and molecular biology of serotonergic receptors has increased exponentially; with each advance it has been necessary to reexamine our assumptions regarding hallucinogen-induced stimulus control. Of particular interest is the hypothesis that a drug may act, at a molecular level, upon multiple receptors to produce, at a behavioral level, a compound discriminative stimulus. The salience of the individual elements of such compound stimuli may be influenced by a variety of experimental factors including training dose, pretreatment time, the state of sensitization of the systems being acted upon, and the nature of the drugs chosen for tests of generalization. This article provides examples of experimental approaches to these complexities using selective agonists and antagonists, depletion-induced sensitization, and antagonist correlation analysis. © 1999 Elsevier Science Inc.

Drug-induced stimulus control Rat Serotonergic receptors LSD DOM Hallucinogens Compound stimuli

THE remarkable behavioral effects of lysergic acid diethylamide (LSD) in humans were first observed by Hofmann in 1943 (28). In the decade that followed it was shown that 5-hydroxytryptamine (5-HT) is the chemical identity both of serotonin and of enteramine, that serotonin is present in the brains of mammalian species, and that the clinical syndrome produced by LSD is similar to that of mescaline (3,4,5-trimethoxyphenylethylamine; (27)]. The last-named observation was later extended to include a second phenethylamine hallucinogen, DOM [3,4-dimethoxy-4-methylamphetamine; (29)]. A serotonergic basis for the actions of LSD was proposed nearly a half century ago on the basis of experiments using isolated smooth muscle (19,52). Furthermore, a number of observations suggested that the phenethylamines and the indoleamines might act via a common mechanism. In human subjects (4,51) as well as in animals (2,47), crosstolerance develops between LSD and mescaline. In addition, both groups of hallucinogens produce similar effects on the firing rate of serotonergic neurons (1) and on the level and rate of turnover of serotonin in the brain (45). Finally, it was known that serotonergic antagonists block some of the nonbehavioral effects of phenethylamine hallucinogens in animals (9,30,33).

With the development of drug-induced stimulus control as a powerful tool for the study of psychoactive drugs, it became possible to rigorously test in animals the hypothesis that indoleamine and phenethylamine hallucinogens act via a common serotonergic mechanism. Following the demonstration that LSD and mescaline could function as discriminative stimuli in the rat (26), it was observed that serotonergic antagonists block the stimulus effects of mescaline (6,48). This observation was later extended to other hallucinogens including lysergic acid diethylamide [LSD; (35,49)], 2,5-dimethoxy-4-methylamphetamine [DOM; (49)], and *N*,*N*-dimethyltryptamine [DMT; (22)].

Although Gaddum and Picarelli described two distinct serotonergic receptors in smooth muscle in 1957 (20), it was not until 1979 that evidence emerged for multiple receptors in brain tissue. Peroutka and Snyder (37) called the subtypes 5-HT_1 and 5-HT_2 and with those designations gave birth to the question of which receptor mediates hallucinogen-

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induced stimulus control in the rat. Based upon the use of ketanserin and pirenperone, antagonists relatively selective for the 5-HT_2 receptor, and a high degree of correlation between affinities for the 5-HT_2 receptor and potency in substituting for DOM-induced stimulus control, Glennon and his colleagues concluded that the 5-HT_2 is the more important (23,24). Furthermore, the correlation between hallucinogenic potency in humans and affinity for the 5-HT_2 receptor implicates this site in hallucinogenesis (24). However, with the discovery of the 5-HT_{2C} receptor (36) it was obvious that the receptor specificity of the hallucinogens was not yet settled. [Although first put in the 5-HT_1 family, recognition that the 5-HT_{1C} and 5-HT_2 receptors are both coupled to phospholipase C, are 80% homologous in the transmembrane regions, and, in contrast with 5-HT_1 receptors, are encoded by genes containing introns, the 5-HT_{1C} receptor was redesignated 5-HT_{2C} with the former 5-HT_2 receptor to be called 5-HT_{2A} (31,32). In the remainder of this article we will use the designation 5-HT_{2C} even if the studies cited employed the earlier term.]

Because of the structural and functional similarities of the 5-HT_{2A} and 5-HT_{2C} receptors, studies of the biochemical efficacies of a series of indoleamines and phenethylamines at these receptors, both in rat choroid plexus and in primary cell culture, were undertaken by Sanders-Bush and her colleagues (39,40). The results indicated that both types of hallucinogens, relative to 5-HT, are partial agonists at the 5-HT_{2C} receptor, and the authors urged consideration of this receptor in the mechanism of action of these drugs. Subsequently, it was reported that, while (+)-LSD stimulates 5-HT_{2C}-mediated phosphoinositide hydrolysis in rat choroid plexus, its nonhallucinogenic congeners, (+)-2-bromo-LSD and lisuride, do not (7). However, it must be noted that agonist activity of lisuride at 5-HT_{2C} receptors in transfected cells has been observed (13).

The remainder of this article will describe two approaches that have been taken in our laboratory to address the question of the relative roles of the 5-HT_{2A} and the 5-HT_{2C} receptors in stimulus control mediated by LSD and DOM. In addition, results of experiments that examine the paradox presented by 5-methoxy-*N*,*N*-dimethyltryptamine (MDMT), will be presented. MDMT is a tryptaminergic hallucinogen that would be expected to act via 5-HT_2 receptors, yet stimulus control in the rat appears to be mediated at the 5-HT_{1A} receptor (43).

ANTAGONIST CORRELATION ANALYSIS

As previously applied to drug-induced stimulus control (14,18) antagonist correlation analysis makes use of a group of chemically unrelated antagonists with unrelated affinities at several different receptors to draw conclusions as to what is and what is not a functionally important receptor interaction. In a study from our laboratory (15), a series of 12 antagonists were examined in terms of their ability to antagonize LSD-induced stimulus control and the generalization of LSD to (−)-DOM in rats trained with LSD as a discriminative stimulus. These behavioral data were then correlated with the respective affinities of the antagonists at 5-HT_{2A} and 5-HT_{2C} receptors. Representative behavioral data are shown in Fig. 1 for pirenperone (10) and the combined behavioral and biochemical data for all of the antagonists are summarized in Table 1.

ID_{50} values obtained from tests of antagonism were analyzed for correlation with binding data describing the 5-HT_{2A} and 5-HT_{2C} receptor affinities for the series of antagonists. As

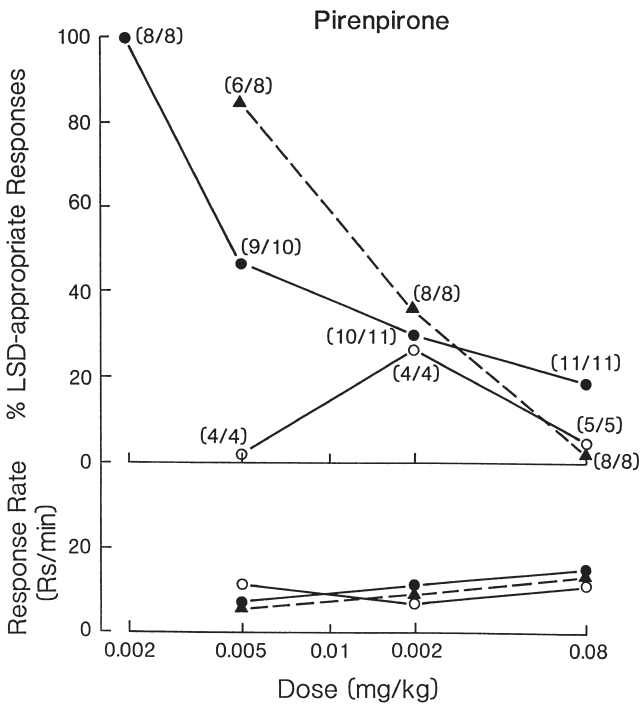

FIG. 1. Dose-inhibition relationship for pirenperone alone (open circles), in the presence of LSD (0.1 mg/kg, 15-min pretreatment time; closed circles), or in the presence of (−)-DOM (0.4 mg/kg, 75-min pretreatment time; closed triangles). The number of subjects completing the test session and the number of subjects participating in each test session is expressed as a ratio adjacent to each datum. Ordinate, upper panel: mean percentage of responses on the LSD-appropriate lever; lower panel: response rate expressed as responses per minute. Abscissa: dose of pirenperone. [From (13), by permission.]

TABLE 1

RECEPTOR AFFINITY VALUES [K_dS] WERE DETERMINED IN VITRO FROM RADIOLIGAND COMPETITION EXPERIMENTS

	K_d[NM]		ID_{50}[mg/kg]	
Antagonist	5-HT_{2A}	5-HT_{2C}	vs. LSD	vs. (−)-DOM
Risperidone	1.42	18.3	0.032	0.016
Pirenperone	1.91	58.9	0.004	0.013
Metergoline	2.24	0.57	0.22	0.11
Ketanserin	3.84	118	0.78	0.3
Loxapine	7.85	17.6	0.56	0.41
LY53857	17.5	14.7	0.99	0.6
Pizotyline	10.3	4.18	3.1	1.5
Spiperone	1.75	4700	0.19	0.057
Cyproheptadine	4.8	20.6	1.8	0.4
Mesulergine	10	3.17	2.3	0.86
Promethazine	124	35.9	NA	57
Thioridazine	93.6	63.1	NA	NA

ID_{50} values were determined for the antagonism of the LSD-appropriate responding elicited by LSD (0.1 mg/kg, 15-min pretreatment time) and (−)-DOM (0.4 mg/kg, 75 min pretreatment time) by a log-logit transformation of the appropriate in vivo dose-inhibition curves. No antagonism is indicated by "NA" [From (14), by permission.]

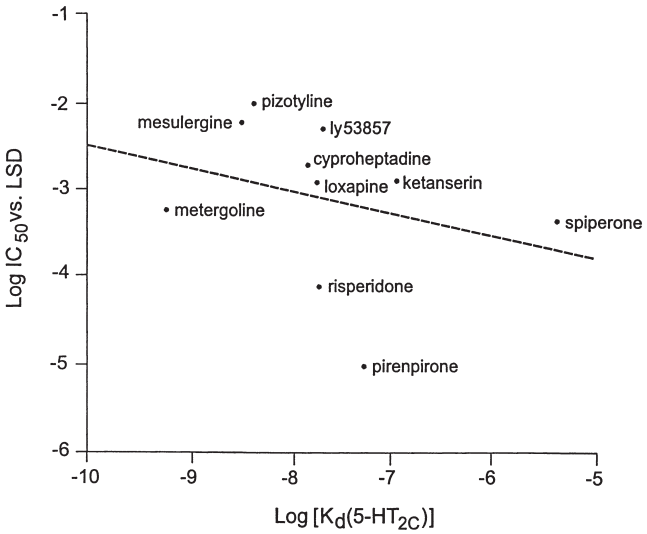

FIG. 2. Correlation between the IC_{50} (mol/kg) for the inhibition of the LSD stimulus and K_i (M) at the 5-HT_{2C} receptor for the series of 10 antagonists. Pearson correlation coefficient (r) = −0.25, nonsignificant.

is seen in Fig. 2 and 3, no significant correlation was observed between the K_i values at the 5-HT_{2C} receptor and the corresponding ID_{50} values for either the blockade of the LSD stimulus ($r = -0.25$) or the blockade of the generalization of LSD to (−)-DOM ($r = -0.29$) for the series of antagonists. In contrast, 5-HT_{2A} affinity was found to correlate significantly with both potency to block the LSD stimulus (Fig. 4; $r = +0.75$, $p < 0.05$) and with potency to antagonize the generalization of LSD to (−)-DOM (Fig. 5; $r = 0.95$, $p < 0.001$).

The data shown in Figs. 2 through 5 led us to conclude (15) that (a) the in vivo potency of the antagonists to block the

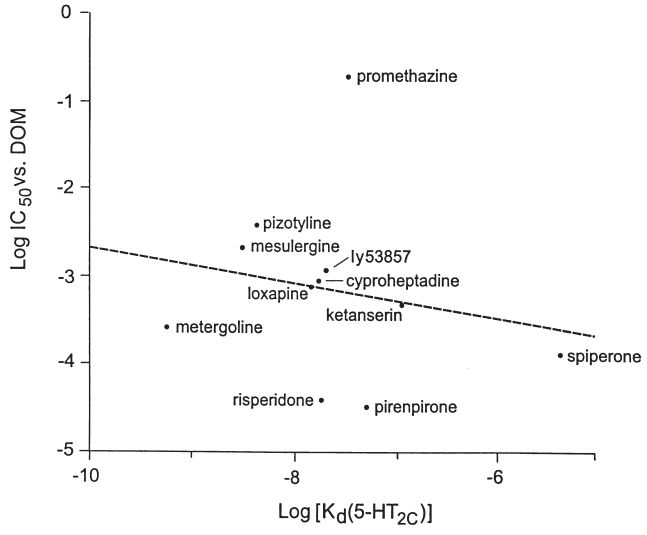

FIG. 3. Correlation between the IC_{50} (mol/kg) for the inhibition of the (−)-DOM–elicited LSD-appropriate responding and K_i (M) at the 5-HT_{2C} receptor for the series of 11 antagonists. Pearson correlation coefficient (r) = −0.25, nonsignificant.

LSD stimulus and the generalization of the LSD stimulus to (−)-DOM is directly proportional to the in vitro affinity of those same antagonists for 5-HT_{2A} receptor, and (b) interactions with 5-HT_{2C} receptors cannot account for the remaining variance in the potencies of the antagonists to block the LSD stimulus or the generalization of the LSD stimulus to (−)-DOM. These data lend support to the hypothesis of Glennon et al. (23,24) that agonist activity at 5-HT_2 receptors is an essential component of the stimulus effects of indoleamine and phenethylamine hallucinogens, and further refine that hypothesis to indicate a predominant role for the 5-HT_{2A} receptor subtype. The latter conclusion is further buttressed by the observation that stimulus control by DOM and its iodo analog are antagonized by drugs that are relatively selective for the 5-HT_{2A} receptor (34,41). In more general terms, antagonist correlation analysis permits conclusions to be drawn regarding behaviorally significant drug–receptor interactions even in the absence of selective ligands.

THE SEROTONIN-DEPLETION HYPERSENSITIVITY PHENOMENON

To further test the hypothesis that the 5-HT_{2A} rather than the 5-HT_{2C} receptor is crucial for the stimulus effects of indoleamine and phenethylamine hallucinogens, we made use of an old observation that depletion of serotonin produces supersensitivity to the effects of hallucinogens. In terms of stimulus control, it had been shown that the stimulus effects both of mescaline (5) and of LSD (8) are potentiated by prior depletion of brain serotonin. However, in a more extensive study of the phenomenon, White et al. (46) observed that the means used to deplete serotonin is a crucial factor. Thus, 5,7-dihydroxytryptamine (5,7-DHT) administered intraventricularly or *p*-chlorophenylalanine (PCPA) intraperitoneally potentiates the LSD cue while depletion using *p*-chloramphetamine (PCA) does not. It was subsequently shown that 5,7-DHT-induced depletion of serotonin upregulates neither the density of central 5-HT_{2A} receptors nor the 5-HT_{2A}-mediated turnover of phosphoinositide (11). In contrast, both the density of 5-HT_{2C} receptors and 5-HT_{2C}-mediated phosphoinositide turnover are upregulated by treatment with 5,7-DHT (12,38). Taken together, these studies imply that it is the 5-HT_{2C} receptor that mediates supersensitivity following serotonin depletion, and suggest that the identification of the pharmacological effect that follows both 5,7-DHT and PCPA, but not PCA, treatments would offer insight into the pharmacological basis for depletion-induced supersensitivity to LSD as well as the mechanism of action of LSD. In an attempt to put behavioral and biochemical data together in a single study, we explicitly tested the hypothesis that upregulation of the 5-HT_{2C} receptor mediates supersensitivity to the LSD stimulus following depletion of serotonin (16).

It is seen in Table 2 that pretreatment with either PCA or PCPA results in significant reduction in the concentrations of 5-HT and its primary metabolite in whole brain. However, the data of Fig. 6 and 7 indicate divergent behavioral effects of the two depleting agents. PCA pretreatment did not result in a shift of the LSD dose–response relationship. In contrast, subjects emitted significantly more LSD-appropriate responses following treatment with PCPA, i.e., the dose–response relationship was shifted to the left, indicating enhanced sensitivity. A biochemical rationale for the distinctly different effects of PCA and PCPA pretreatments on stimulus control by LSD is offered by the data of Table 3. There it is seen that 5-HT_{2A}-mediated phosphoinositide hydrolysis is not altered following treatment with either depleting agent. However, 5-HT_{2C}-medi-

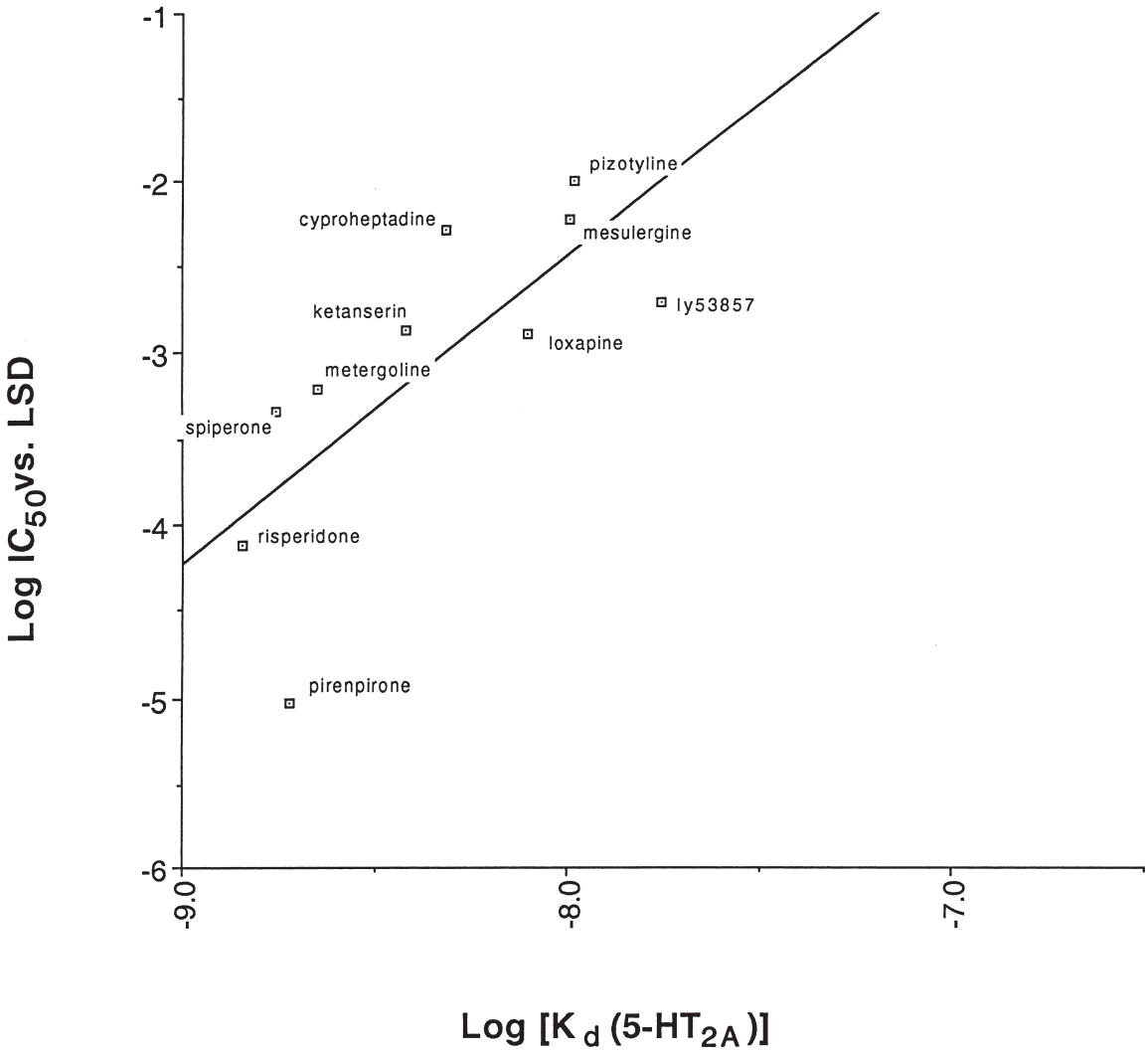

FIG. 4. Correlation between the IC_{50} (mol/kg) for the inhibition of the LSD stimulus and K_i (M) at the 5-HT_{2A} receptor for the series of 10 antagonists. Pearson correlation coefficient (r) = +0.75, $p < 0.05$. [From (13), by permission.]

ated phosphoinositide hydrolysis was significantly greater in the choroid plexus of PCPA-treated rats, while PCA treatment had no effect on 5-HT_{2C}-mediated PI hydrolysis.

The data of Figs. 6 and 7 and Table 2 are parsimoniously explained by the hypothesis that upregulation of the 5-HT_{2C} receptor as reflected in increased PI hydrolysis following serotonin depletion by PCPA results in heightened sensitivity to the discriminative stimulus induced by LSD. When considered in the context of previous studies employing either selective antagonists (34,41) or antagonist correlation analysis [(15) and above], which have demonstrated that agonist interactions with the 5-HT_{2A} receptor predominately mediate the stimulus properties of hallucinogens, the present data are consistent with the hypothesis that agonist interactions with 5-HT_{2C} receptors play a significant modulatory role (25).

THE PARADOX OF 5-METHOXY-*N*,*N*-DIMETHYLTRYPTAMINE

In light of the considerable evidence cited above that 5-HT_2 receptors mediate stimulus control by LSD, DOM, and related drugs, the cue induced by the indoleamine, 5-methoxy-*N*,*N*-dimethyltryptamine (MDMT), is puzzling. Although its hallucinogenicity is not in doubt (42), in the most extensive analysis to date of stimulus control in the rat by MDMT Spencer et al. (43) concluded that "the 5-HT_{1A} receptor subtype is strongly involved. . . ." Against that background, we set out to test the hypothesis that MDMT, whatever its activity at 5-HT_{1A} receptors, also produces functionally significant effects at 5-HT_2 receptors (50). One advantage we had over the earlier workers was the availability of the drug WAY-100635, a selective, pure antagonist at 5-HT_{1A} receptors (17).

The dose–response relationship for MDMT and the effects of the antagonists WAY-100635 and pirenperone are shown in Fig. 8. At the two higher doses of MDMT, against which the antagonists were examined, WAY-100635 was clearly the more effective drug. We are unaware of any previous reports of the antagonism by WAY-100635 of stimulus control by MDMT but, given the high degree of selectivity of WAY-100635 for the 5-HT_{1A} receptor (17), the data of Fig. 8 strongly support an effect mediated by that receptor. None-

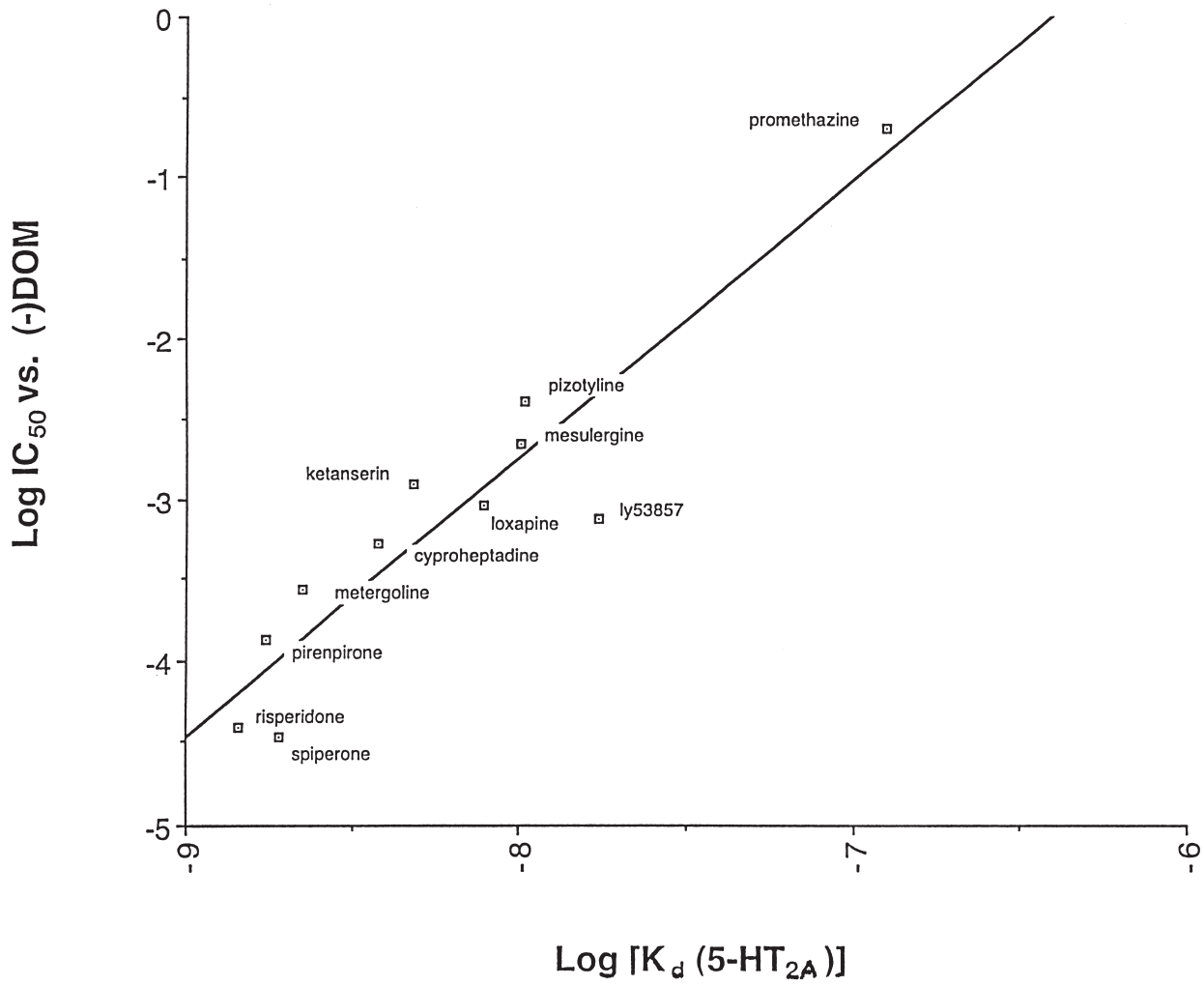

FIG. 5. Correlation between the IC_{50} (mol/kg) for the inhibition of the (−)-DOM–elicited LSD-appropriate responding and K_i (M) at the 5-HT_{2A} receptor for the series of 11 antagonists. Pearson correlation coefficient (r) = +0.95, $p < 0.001$. [From (13), by permission.]

theless, pirenperone produced an intermediate degree of antagonism when given in combination with the training dose of MDMT. When the prototypical 5-HT_{1A} agonist, 8-OH-DPAT, was tested in rats trained with MDMT (Fig. 9), 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 pirenperone had no effect, WAY-100635 completely antagonized the substitution of 8-OH-DPAT for MDMT. 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. In the landmark study by Spencer et al. (43), complete generalization of MDMT to the 5-HT_{1A}-selective agonist, 8-OH-DPAT, was observed. That finding is fully replicated in Fig. 9, 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.

TABLE 2

THE EFFECT OF PCPA AND PCA ON WHOLE BRAIN CONCENT RATIONS OF 5-HT AND 5-HIAA

	Control	PCA	PCPA
5-HT	9.32 (0.53)	5.80 (0.40)*	5.05 (0.193)*
5-HIAA	3.14 (0.27)*	0.763 (0.13)*	0.186 (0.031)*

Concentrations (ng/mg) represent the means of five individual determinations. Standard errors are in parentheses.

*Indicates significant difference from the control values by Student–Newman–Keuls test ($p < 0.01$). [From (15), by permission.]

Figure 10 shows the tests of generalization of MDMT 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. 8, the partial generalization of MDMT to (−)-DOM was com-

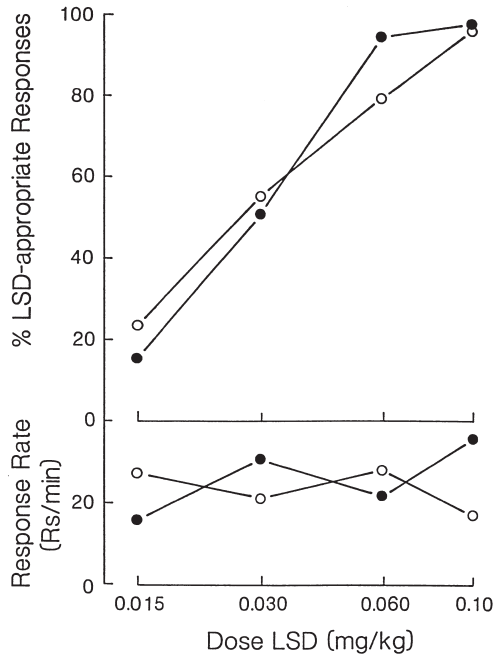

FIG. 6. The effect of PCA-induced serotonin depletion on the LSD dose–response relationship. Closed circles represent results from nine subjects following treatment with PCA. Open circles represent nine parallel control subjects. Abscissa: dose of LSD; Ordinate: percentage of responses emitted on the LSD-appropriate lever. [From (14), by permission.]

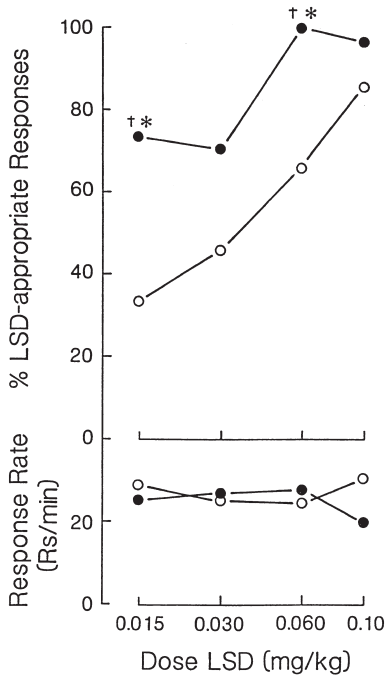

FIG. 7. The effect of PCPA-induced serotonin depletion on the LSD dose–response relationship. Closed circles represent results from nine subjects following treatment with PCPA. Open circles represent nine parallel control subjects. Abscissa: dose of LSD; Ordinate: percentage of responses emitted on the LSD-appropriate lever. *Indicates significant difference from parallel control ($p < 0.05$, Wilcoxon's signed-ranks test), cross represents significant difference from the same subjects prior to PCPA treatment ($p < 0.05$, paired application of Wilcoxon's signed-ranks test). [From (14), by permission.]

pletely blocked by pirenperone, while WAY-100635 was without antagonistic effects.

When animals trained with (−)-DOM were tested with MDMT via the intraperitoneal route, no statistically significant generalization occurred at any dose (data not shown). However, when the same (−)-DOM–trained rats were tested with MDMT administered via the subcutaneous route (Fig. 11), 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 MDMT for (−)-DOM, the suppression of response rates was significantly antagonized. When pirenperone was given in combination with MDMT, responding was completely suppressed; hence, stimulus control could not be assessed. However, the administration of both WAY-100635 and pirenperone in combination with MDMT resulted in a restoration of responding and a significant antagonism of the partial substitution of MDMT for (−)-DOM.

In summary, the present data indicate that the indoleamine hallucinogen, MDMT, 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. (43), 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 MDMT-induced stimulus control. However, the present data indicate as well that MDMT induces a compound stimulus that includes an element mediated by 5-HT_2 receptors. As predicted by the Ator hypothesis (3), 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 (15,21,23,24), and that human hallucinogenic activity likewise arises at those receptors (32), 5-HT_{1A}-mediated stimulus control by MDMT presents a paradox. Indeed, Strassman et al. (44) have suggested that the dimethyltryptamines may be unique among classic hallucinogens. Based upon the

TABLE 3

5-HT_{2A} AND 5-HT_{2C}-MEDIATED PHOSPHOINOSITIDE HYDROLYSIS IN RESPONSE TO SUPRAMAXIMAL (250 μM AND 10 μM) CONCENTRATIONS OF 5-HT

	Percent Stimulation Above Basal			
Receptor (Tissue)	$Control_1$	PCPA	$Control_2$	PCA
5-HT_{2A} (frontal cortex)	66.1 (6.1)	67.3 (7.6)	71.0 (2.6)	67.5 (8.4)
5-HT_{2C} (choroid plexus)	654 (82)	960 (111)*	739 (144)	796 (78)

Responses are expressed in percent stimulation above basal (100 × (stimulated-basal)/basal). The reported values are the averages of 7–10 individual determinations. Average levels of basal [^{3}H]IP information in the choroid plexus were 13,700 (±1,600) and 12,000 (±1,900) cpm/mg protein for the PCPA and PCA experiments, respectively.

*Indicates a significant difference from parallel control value ($p < 0.05$ by Student's t-test). [From (49), by permission.]

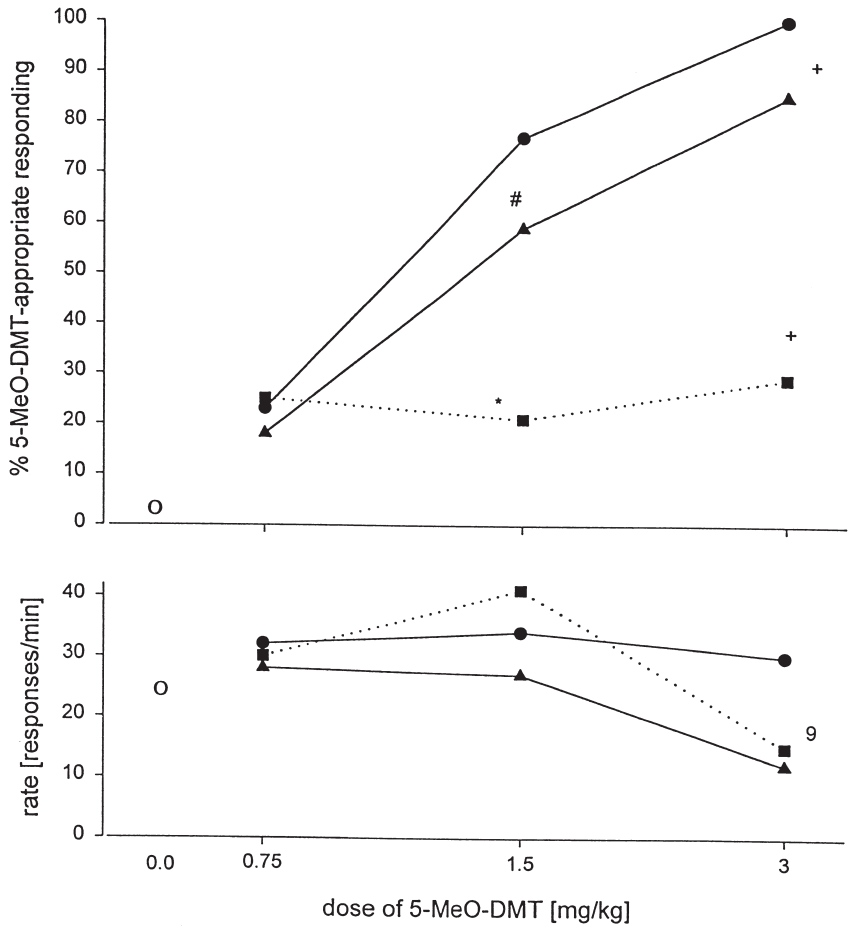

FIG. 8. Dose–response relationship for MDMT (circles) in rats trained with MDMT (3 mg/kg) as a discriminative stimulus and the interaction of MDMT with pirenperone (0.16 mg/kg; triangles), and with WAY-100635 (0.3 mg/kg; squares). Pirenperone was injected IP, 60 min before testing. The point at a dose of 0.0 mg/kg is for saline control sessions. The points at 1.5 and 3.0 mg/kg of MDMT represent the mean of two determinations in each of the subjects. [From (49), by permission.] *Significant difference from MDMT alone. *#Significant difference from saline. +Significant difference from MDMT and saline.

present data, we suggest as an alternative that MDMT differs from LSD and DOM with respect to the serotonergic element which mediates stimulus control in the rat but that it shares with those drugs a functionally significant interaction with 5-HT_2 receptors.

EPILOGUE

The mists of time have obscured the details of mankind's first hallucinogenic adventures with crude botanical materials. However, it may reasonably be argued that the modern era began in 1896 with Heffter's isolation of mescaline from *Lophophora williamsii* and Spath's determination 20 years later of its structure as 3,4,5-trimethoxyphenylethylamine. Only then could one speak with confidence of drug-induced hallucinations. The second stride of the modern era was taken by Hofmann in 1943, with his discovery of the hallucinogenic effects of lysergic acid diethylamide. The purported ability of LSD and mescaline to enhance self-knowledge, to expand the powers of the mind, and to stimulate creativity was proclaimed by figures ranging from Aldous Huxley to Timothy Leary to George Harrison to Kary Mullis. A portion of their legacy is found in survey data from the United States, which indicate a 50% increase in the use of hallucinogens between 1992 and 1995 among those age 17 and younger. As fascinating as is the question of how these drugs so profoundly alter the mental state of humans and as socially significant as is their abuse, there is another reason for continued interest. Perhaps unique among drugs chosen for use for their pleasurable effects, an understanding of the mechanisms of action of hallucinogens might contribute to solving the puzzle of psychosis, a major human affliction. For example, the observation that atypical antipsychotics such as clozapine and risperidone have high affinity for serotonergic receptors has given new life to the old idea that there may be a mechanistic connection between exogenous hallucinogens and the endogenous hallucinogenic processes of psychosis (see also Goudie, this volume).

Although it is generally assumed by those who employ nonhuman subjects in the study of these drugs that the biological events that precede and accompany chemically induced hallucinations in humans are similar in lower species, some la-

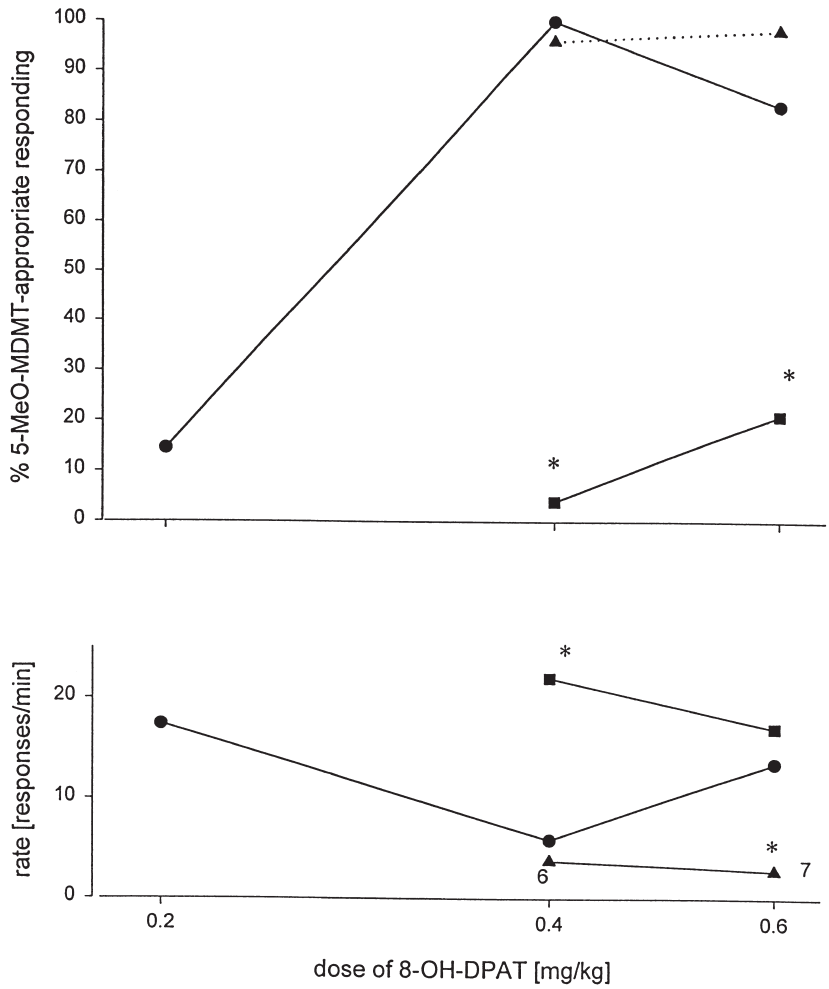

FIG. 9. Dose–response relationship for 8-OH-DPAT (circles; IP, 15 min before testing) in rats trained with MDMT as a discriminative stimulus and the interaction of 8-OH-DPAT with pirenperone (triangles) and with WAY-100635 (squares). *Significantly different from 8-OH-DPAT alone. All other details are as in Fig. 8. [From (49), by permission.]

ment the fact that we may never know if there exists a counterpart in animals of the human hallucinogenic experience. In this regard, it is our view that experiments in nonverbal species can only point the way to hypotheses testable in humans, and it is unfortunate that at various times in various places research in human subjects has been stunted by restrictive government policies. Indeed, it is partly for this reason that the study of hallucinogen-induced stimulus control in animals urges itself upon us. In contrast with earlier behavioral methods that were applied to these drugs, stimulus control offers an intuitively attractive, sensitive, and specific procedure that is well-suited to the discovery of fundamental pharmacological mechanisms. Given the guidance of ever more sophisticated chemical, biochemical, and molecular biological techniques, the continued application of the techniques of drug-induced stimulus control to intact animals remains exciting in its promise.

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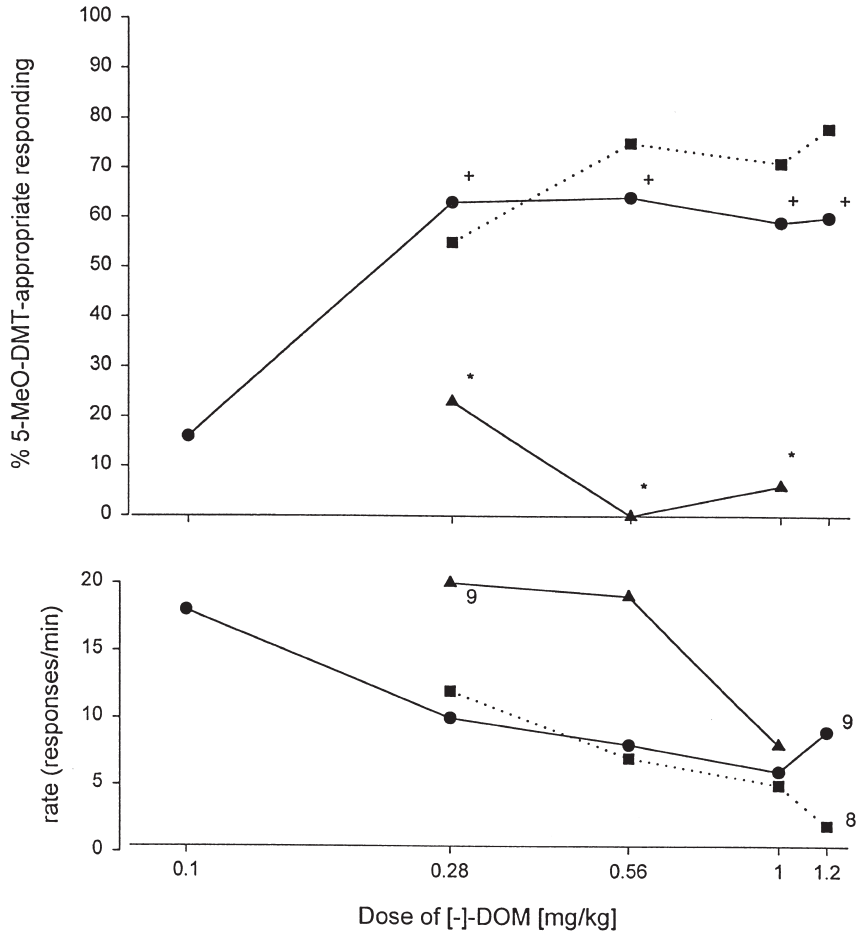

Fig. 10. Dose–response relationship for (−)-DOM (circles) in rats trained with MDMT (3 mg/kg) as a discriminative stimulus and the interaction of (−)-DOM with pirenperone (triangles) and with WAY-100635 (squares). Each point on the dose–response curve for MDMT represents the mean of three determinations in all subjects. (−)-DOM was administered 75 min before testing. *Significant difference from DOM alone. All other details are as in Fig. 8. [From (14), by permission.]

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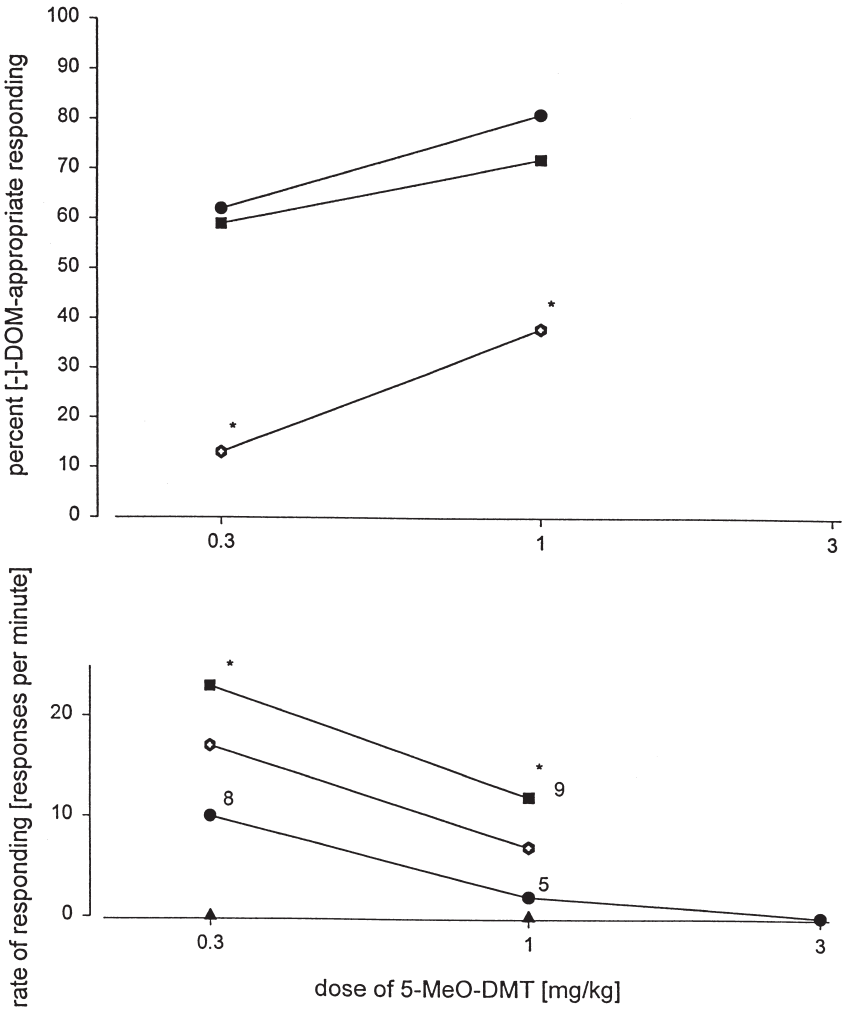

FIG. 11. Dose–response relationship for MDMT (circles) administered SC to rats trained with (−)-DOM as a discriminative stimulus and the interaction of MDMT with pirenperone (triangles), WAY-100635 (squares), and the combination of pirenperone and WAY-100635 (hexagons). *Significantly different from MDMT alone. All other details are as in Fig. 8. [From (14), by permission.]

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