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ORIGINAL INVESTIGATION

The roles of 5-HT_{1A} and 5-HT_2 receptors in the effects of 5-MeO-DMT on locomotor activity and prepulse inhibition in rats

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Abstract
Rationale The hallucinogen 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) is structurally similar to other indoleamine hallucinogens such as LSD. The present study examined the effects of 5-MeO-DMT in rats using the Behavioral Pattern Monitor (BPM), which enables analyses of patterns of locomotor activity and exploration, and the prepulse inhibition of startle (PPI) paradigm.
Objectives A series of interaction studies using the serotonin (5-HT)$_{1A}$ antagonist WAY-100635 (1.0 mg/kg), the 5-HT_{2A} antagonist M100907 (1.0 mg/kg), and the 5-HT_{2C} antagonist SER-082 (0.5 mg/kg) were performed to assess the respective contributions of these receptors to the behavioral effects of 5-MeO-DMT (0.01, 0.1, and 1.0 mg/kg) in the BPM and PPI paradigms.
Results 5-MeO-DMT decreased locomotor activity, investigatory behavior, the time spent in the center of the BPM chamber, and disrupted PPI. All of these effects were antagonized by WAY-100635 pretreatment. M100907 pretreatment failed to attenuate any of these effects, while SER-082 pretreatment only antagonized the PPI disruption produced by 5-MeO-DMT.
Conclusions While the prevailing view was that the activation of 5-HT_2 receptors is solely responsible for hallucinogenic drug effects, these results support a role for 5-HT_{1A} receptors in the effects of the indoleamine hallucinogen 5-MeO-DMT on locomotor activity and PPI in rats.

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Introduction

For years, indigenous Amazonian tribes in South America have made hallucinogenic preparations from various barks, leaves, and vines, such as Myristicaceae bark (McKenna et al. 1984; Schultes 1979). Analysis of these samples has revealed different hallucinogenic compounds, including 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT), a member of the dimethyltryptamine subclass of the indoleamine hallucinogens (Glennon and Rosecrans 1982; Holmstedt et al. 1980) that is a known hallucinogen in humans (Shulgin and Shulgin 1997). 5-MeO-DMT is also found in some concoctions of the sacramental tea *Ayahuasca* and other plant extracts used in ritual settings (Holmstedt et al. 1980; Schultes and Raffauf 1995). 5-MeO-DMT is the most potent member of this subclass, about ten times more active than *N*,*N*-dimethyltryptamine (DMT) (Glennon and Rosecrans 1982). In animal studies, 5-MeO-DMT is more practical to use as the prototypical agent because it is longer-acting than DMT.

A variety of behavioral effects of relatively high doses of 5-MeO-DMT were noted in rodents, including components of the serotonin (5-HT) syndrome, such as head shaking or twitching, forepaw treading, flat-body posture, Straub tail, and hindlimb abduction. These effects are also produced by hallucinogenic compounds that activate central 5-HT systems, such as the 5-HT_2 agonists, 1(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) and 2,5-dimethoxy-4-methylamphetamine (DOM), and 5-HT_{1A} agonists (Arnt and Hyttel 1989; Berendsen et al. 1989; Bervoets et al. 1990;

Darmani et al. 1990; Eison and Wright 1992; Lucki and Frazer 1982; Lucki et al. 1984; Matthews and Smith 1980; Scott et al. 1994; Sloviter et al. 1978; Smith and Peroutka 1986; Tricklebank et al. 1985). The lower lip retraction produced by 5-MeO-DMT, however, is thought to be due to the activation of 5-HT_{1A} rather than 5-HT_2 receptors because it is only produced by 5-HT_{1A} agonists, such as 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (Berendsen et al. 1989). In tests of drug discrimination, 5-MeO-DMT was shown to generalize to other hallucinogens, such as LSD, DOM, DMT, and mescaline (Glennon et al. 1979, 1980, 1983; Spencer et al. 1987). This fact is not surprising because 5-MeO-DMT has demonstrated agonist activity for the 5-HT_2 receptors most commonly associated with hallucinogenic activity (Boulenguez et al. 1991; Dumuis et al. 1987; Glennon et al. 1980, 1984; McClue et al. 1989; McKenna et al. 1990; Titeler et al. 1988). 5-MeO-DMT, however, is also an agonist at 5-HT_{1A} receptors. Winter et al. (2000) demonstrated that in rats trained to discriminate 5-MeO-DMT from saline, this effect was blocked by the 5-HT_{1A} antagonist WAY-100635, but not by a 5-HT_2 antagonist. Thus, in its activity and effects, 5-MeO-DMT appears to be a mixed 5-$HT_{1A/2}$ agonist, like LSD and DMT (Boulenguez et al. 1991; Dumuis et al. 1987; McClue et al. 1989; McKenna et al. 1990).

The prevailing view has been that the activation of 5-HT_2 receptors is solely responsible for hallucinogenic drug effects. This conclusion was reached for several reasons: there is a strong correlation between 5-HT_2 binding affinity and hallucinogenic potency; the two classes of traditional hallucinogens, indoleamines and phenalkylamines, differ in structure but share one common mechanism of action (stimulation of 5-HT_2 receptors); and selective 5-HT_{1A} agonists were not shown to be hallucinogenic in humans (Glennon et al. 1984; Titeler et al. 1988). Nevertheless, because most of the evidence supporting the role of 5-HT_2 receptors in hallucinogen action is derived primarily from studies of phenalkylamine drugs, the 5-HT_{1A} receptor agonist activity of indoleamines such as LSD and 5-MeO-DMT may contribute to their behavioral effects, either directly or through a functional interaction with 5-HT_2 receptors (Geyer and Krebs 1994; Glennon et al. 1984; Krebs and Geyer 1994; Krebs-Thomson and Geyer 1998; Titeler et al. 1988).

A variety of hallucinogens and other psychoactive drugs were tested using standardized procedures in the rat Behavioral Pattern Monitor (BPM). The BPM is a combined activity and holeboard chamber that enables the analyses of quantitative and qualitative changes in patterns of locomotor and investigatory activity (Geyer 1990). Hallucinogens have characteristic effects on locomotor and exploratory behavior in rats exposed for the first time to the BPM. Specifically, hallucinogens decrease both locomotor activity and investigatory holepokes, while increasing avoidance of the central portion of the BPM chamber (Geyer and Krebs 1994). This pattern of behavior was described as a potentiation of neophobia and agoraphobia because of the increased avoidance of novel and central areas (Geyer and Krebs 1994). In addition to LSD, both phenalkylamine and indoleamine hallucinogens produce similar behavioral profiles, while a variety of other psychoactive drugs produce different behavioral profiles in this paradigm (Geyer and Krebs 1994).

We have tested the effects of LSD in the BPM with the 5-HT_{2A} antagonist M100907, the 5-HT_{2C} antagonist SER-082, and the 5-HT_{1A} antagonist WAY-100635 (Krebs-Thomson et al. 1998). LSD decreased locomotor activity, exploratory behavior, and affected the pattern of locomotion. It is interesting to note that not all three antagonists attenuated these effects. While the decrement locomotor activity produced by LSD was attenuated only by the 5-HT_{1A} antagonist WAY-100635, the effect of LSD on exploration was antagonized only by the 5-HT_{2A} antagonist M100907 (Krebs-Thomson et al. 1998). In contrast, the effect of LSD on locomotor patterns was reduced by all three antagonists. Thus, for the mixed 5-$HT_{1A/2A/2C}$ agonist LSD, effects on the amount of locomotor activity are due to 5-HT_{1A} receptors, effects on exploratory behavior are due to 5-HT_{2A} receptors, and the quality of the behavioral organization of the activity are due to multiple 5-HT receptors (Krebs-Thomson et al. 1998). Other researchers have found that when rats are tested during the light phase of their cycle, LSD produced *hyperactivity* (Ouagazzal et al. 2001). This effect of LSD was also antagonized by M100907 pretreatment.

Sensorimotor gating has been extensively examined in rodents using prepulse inhibition of startle (PPI) as an operational measure (Geyer et al. 2001). Sensorimotor gating is one of the processes by which an organism screens or filters the large flow of information from its surroundings (Braff and Geyer 1990). PPI occurs when a weak nonstartling stimulus (prepulse) precedes a startling stimulus (pulse) and inhibits the startle response (Hoffman and Ison 1980). Indoleamine-derived hallucinogens, such as LSD and 5-MeO-DMT, do not have consistent effects on PPI in rats, except at high doses (Nanry and Tilson 1989; Ouagazzal et al. 2001; Rigdon and Weatherspoon 1992). While there are no published accounts of 5-MeO-DMT testing in PPI with subtype-specific 5-HT antagonists, Ouagazzal et al. (2001) demonstrated that a high dose of LSD (100 μg/kg) disrupted PPI and that this effect was antagonized by a 0.5-mg/kg, but not a 1.0-mg/kg, dose of the 5-HT_{2A} antagonist M100907. The 5-HT_{1A} and 5-HT_{2C} antagonists WAY-100135 and SER-082, respectively, failed to antagonize this effect of LSD (Ouagazzal et al. 2001).

In the present series of interaction studies, the 5-HT_{1A} antagonist WAY-100635, the 5-HT_{2A} antagonist M100907,

and the 5-HT_{2C} antagonist SER-082 were used to assess the respective contributions of these receptors to the effects of 5-MeO-DMT in the BPM and PPI paradigms.

Materials and methods

Animals

Naive male Sprague–Dawley rats (Harlan Industries, Indianapolis, IN, USA) (275 to 300 g) were housed in pairs under a 12-h reverse light cycle (lights off at 0700 hours) with ad libitum food and water. Animals were allowed to acclimatize for approximately 1 week after arrival. Principles of laboratory animal care were followed as well as specific laws of the United States.

Behavioral testing

BPM

Behavior was measured in the BPM, a 30.5×61.0-cm black Plexiglas chamber equipped with 2.5-cm holes in the walls and floor, as detailed elsewhere (Geyer et al. 1986). Photocells in each hole detect investigatory nosepokes (holepokes). A touchplate, 15.2 cm above the floor, allows detection of rearings when the animal made contact between the metal floor and the metal touchplate. A 4×8-grid of infrared photobeams detects the animal's position in an *X*–*Y* plane. A computer continuously monitors all photobeams and the touchplate and stores the data for later analysis.

Startle chambers

Four startle chambers (SR-LAB system, San Diego Instruments, San Diego, CA, USA) described elsewhere (Mansbach et al. 1988) were used. Briefly, the startle chambers consist of a Plexiglas cylinder, 8.2 cm in diameter, resting on a 12.5×25.5-cm Plexiglas frame within a sound-attenuated ventilated enclosure. Acoustic startle was produced by a loudspeaker mounted 24 cm above the Plexiglas cylinder. A piezoelectric accelerometer on the base of the cylinder frame detected and transduced vibration, which was digitized and recorded by an interface unit and microcomputer. Sound levels [dB (A) scale] and accelerometer sensitivities within each chamber are calibrated regularly and remained constant throughout the experiment.

Analysis

BPM

The raw data were reduced to the X and Y coordinates of the rat in the chamber, the occurrence of holepokes or rearings, and the amount of time spent at a particular coordinate or performing a particular behavior. Further analyses produced specific measures of behavior (for details, see Geyer et al. 1986). Locomotor activity was quantified by the number of crossings between any of eight equal square sectors within the BPM (crossings) as a measure of horizontal locomotion. Time spent in the center of the chamber was quantified by the time spent in the center. The number of holepokes was calculated. Data were examined in 10-min time resolutions. Data were analyzed using three-way ANOVA with pretreatment and treatment as between-factors and time as a repeated measure. Specific post hoc comparisons between selected groups were done using Tukey's studentized range method. Significance was demonstrated by surpassing an alpha level of 0.05.

Startle and PPI

Animals were initially tested in a brief baseline session to create treatment groups matched for levels of startle and PPI. The test session utilized consisted of the following components: a 5-min acclimation period to a 65-dB background noise, which continued throughout the entire session; 20 PULSE-ALONE trials in which a 40-ms 120-dB broadband noise burst was presented (P120); 30 PREPULSE+PULSE trials in which the onset of a 20-ms broadband noise preceded the onset of the 120-dB PULSE by 100 ms [10 prepulses each of 68, 71, and 77 dB (or 3, 6, and 12 dB above background)]; and 10 NOSTIM trials in which no stimuli were presented. Trials were presented in a pseudorandom order with an average 15-s (9–21 s range) intertrial interval. Five P120 trials were presented at the beginning and the end of the test session (for a total of 60 trials), but were not used in the calculation of PPI values (Bakshi et al. 1998).

The mean response for each trial type was calculated by averaging the 100 1-ms readings that began at the onset of the startle (P120) stimulus. The level of PPI was calculated as a percentage score for each prepulse intensity (%PPI=100−{[(startle response for prepulse+pulse trial)/(startle response for Pulse-Alone trial)]×100}). PPI data were analyzed using a four-way ANOVA with pretreatment and treatment as between-subjects factors with time and prepulse intensity as repeated measures. Where the time factor was not significant, three-way ANOVAs collapsed across time were performed, followed, when appropriate, by Tukey's post hoc analyses. The average response to all the P120 trials was analyzed in a separate two-factor (pretreatment and treatment) ANOVA to assess baseline startle reactivity. For all variables, significance was demonstrated by surpassing an alpha level of 0.05.

Procedure

One day before BPM studies, animals were taken to the testing room, weighed, handled briefly, placed in a clear Plexiglas box (24×46 cm) for approximately 30 s, and then returned to their cages in the animal room. On the testing day, rats were tested for 60 min in dark BPM chambers. For both BPM and startle tests, rats were brought to the testing room during the dark phase of their light cycle and allowed to sit for 60 min before receiving pretreatment injections.

Drugs

Drugs used were 5-MeO-DMT (Sigma Biochemicals, St. Louis, MO, USA); (*R*)-(+)-(2,3-dimethoxyphenyl)-1-[2-(fluorophenyl)ethyl]-4-piperidinemethanol (M100907; Hoechst Marion Roussel, Cincinnati, OH, USA); (+)-*cis*-4,5,7a,8,9,10,11,11a-octahydro-7*H*-10methylindol[1,7-*bc*][2,6]-naphthyridine (SER-082; J. Nozulak, Novartis, Basel, Switzerland); *N*-*N*-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride (WAY-100635; Wyeth-Ayerst, UK). 5-MeO-DMT was dissolved in nitrogen-purged saline. M100907 was dissolved in a solution of Tween 80 and saline. All drugs were administered subcutaneously in a volume of 1 ml/kg. For all studies, pretreatment and treatment injections were administered 30 and 10 min, respectively, before placement of the rats in the BPM or startle chamber.

Results

BPM studies

Experiment 1 Sixty-four rats (n=8/group) were treated with either vehicle or WAY-100635 (1.0 mg/kg) 20 min before injections of either vehicle or 5-MeO-DMT (0.01, 0.1, or 1.0 mg/kg). Doses of 5-MeO-DMT were based on previous dose–response studies (Thomson 1996).

Results and discussion There was a significant interaction between WAY-100635 pretreatment and 5-MeO-DMT treatment for crossings, a measure of the amount of locomotor activity [$F(3,56)=7.72$, $p=0.00$]. There was also a significant interaction of pretreatment and treatment with time [$F(15,280)=9.18$, $p=0.00$]. Accordingly, and based on previous studies with hallucinogens (Krebs and Geyer 1994; Krebs-Thomson and Geyer 1996, 1998), we further examined the first 10 min of testing. Close examination of the full hour of testing (data not shown) and extensive experience with the time course of hallucinogen effects (Krebs and Geyer 1994; Krebs-Thomson and Geyer 1996, 1998; Krebs-Thomson et al. 1998) convinced us that the initial 10 min of testing adequately represents the drug effects.

Again, there was a significant interaction between WAY-100635 pretreatment and 5-MeO-DMT treatment for the first 10 min of testing for crossings [$F(3,56)=19.30$, $p=0.00$]. Specific comparisons revealed that both the 0.1 and 1.0 mg/kg doses of 5-MeO-DMT significantly decreased crossings, compared to the vehicle group. While the highest dose was not affected by WAY-100635 pretreatment, the 0.1 mg/kg 5-MeO-DMT group was significantly different from the WAY-100635/0.1 mg/kg 5-MeO-DMT group, indicating antagonism of the effects of 0.1 mg/kg of 5-MeO-DMT by WAY-100635 pretreatment (Fig. 1).

There were significant effects of both WAY-100635 pretreatment [$F(1,56)=4.49$, $p=0.04$] and 5-MeO-DMT treatment [$F(3,56)=14.23$, $p=0.00$] on holepokes, a measure of investigatory activity. There were significant interactions with time for pretreatment [$F(5,280)=3.37$, $p=0.01$] and treatment [$F(15,280)=3.94$, $p=0.00$]. Based on these significant interactions with time and the analysis done for the crossings measure, we analyzed the first 10 min. For the initial 10 min of testing, there was a significant interaction between WAY-100635 pretreatment and 5-MeO-DMT treatment [$F(3,56)=3.11$, $p=0.03$]. Specific comparisons revealed that the 0.1- and 1.0-mg/kg doses of 5-MeO-DMT differed from the vehicle (Fig. 2). The decrease in investigatory activity produced by 0.1 mg/kg of 5-MeO-DMT was antagonized by WAY-100635, although the effect of the higher dose of 5-MeO-DMT was not (Fig. 2).

There was a significant effect of 5-MeO-DMT treatment for center duration [$F(3,56)=13.73$, $p=0.00$]. There were also significant interactions of WAY-100635 pretreatment [$F(5,280)=2.76$, $p=0.02$] and 5-MeO-DMT treatment [$F(15,280)=2.24$, $p=0.01$] with time. During the first 10 min of testing, there was a significant interaction between WAY-100635 and 5-MeO-DMT for time spent in the center of the chamber [$F(3,56)=6.90$, $p=0.00$]. Specific comparisons revealed that the 0.1- and 1.0-mg/kg doses of 5-MeO-DMT significantly decreased center duration (Fig. 3). The decrement produced by the 0.1-mg/kg dose of 5-MeO-DMT was antagonized by WAY-100635 pretreatment.

Experiment 2 Sixty-four rats (n=8/group) were treated with either vehicle or 1.0 mg/kg M100907 20 min before injection of either vehicle or 5-MeO-DMT (0.01, 0.1, or 1.0 mg/kg).

Results and discussion There was a significant effect of 5-MeO-DMT treatment on crossings [$F(3,56)=25.51$, $p=0.00$] and a significant interaction of 5-MeO-DMT with time [$F(15,280)=20.10$, $p=0.00$]. In the initial 10 min of testing, there was a significant effect of 5-MeO-DMT

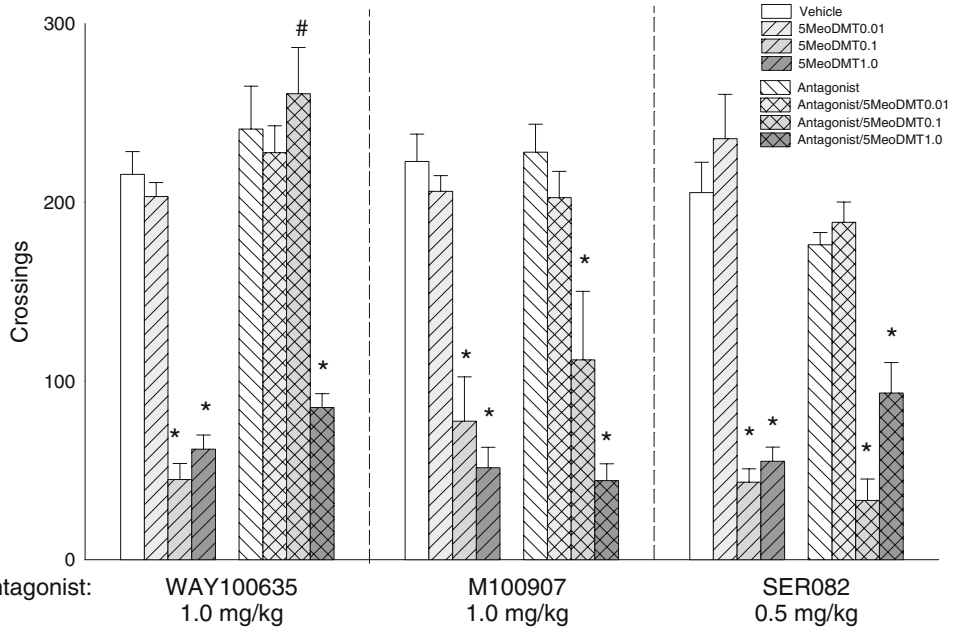

Fig. 1 Antagonist effects on 5-MeO-DMT-induced hypoactivity. 5-MeO-DMT decreased crossings, a measure of locomotor activity. *Dashed lines* divide the three separate experiments. In each experiment, the 0.1- and 1.0-mg/kg doses of 5-MeO-DMT significantly reduced crossings. Only WAY-100635 pretreatment significantly attenuated the effect of 0.1 mg/kg of 5-MeO-DMT. Both M100907 and SER-082 pretreatments failed to alter the hypoactivity produced by 5-MeO-DMT. Data are presented as group means±SEM for the initial 10 min of testing. *$p<0.05$, group is different from its vehicle control group. #$p<0.05$, group is different from its vehicle/5-MeO-DMT group

[$F(3,56)=37.97$, $p=0.00$], but no significant interaction with M100907. Specific comparisons revealed that the 0.1- and 1.0-mg/kg doses of 5-MeO-DMT reduced crossings (Fig. 1) and that this effect was not attenuated by M100907 pretreatment.

There was a significant interaction between M100907 pretreatment and 5-MeO-DMT treatment on holepokes [$F(3,56)=3.31$, $p=0.03$]. There was a significant interaction of 5-MeO-DMT treatment with time [$F(15,280)=4.13$, $p=0.00$], leading us to analyze the first 10 min of testing. In the initial 10 min, there was a significant effect of 5-MeO-DMT treatment [$F(3,56)=25.19$, $p=0.00$], but no significant interaction. Specific comparisons revealed that the 0.1- and 1.0-mg/kg doses of 5-MeO-DMT significantly reduced holepokes (Fig. 2), but this effect was not antagonized by M100907 pretreatment. Examination of the data suggests that the significant interaction, although not present in the analysis of the initial 10 min, was probably due to a pattern in which the lowest dose of 5-MeO-DMT nonsignificantly increased holepokes, while the opposite tendency was evident after M100907 pretreatment. Such a pattern may reflect a subtle and complex interaction of low dose 5-MeO-DMT with M100907 pretreatment in their effects on investigatory activity.

There were significant effects of M100907 pretreatment [$F(1,56)=5.35$] and 5-MeO-DMT treatment [$F(3,56)=6.66$]

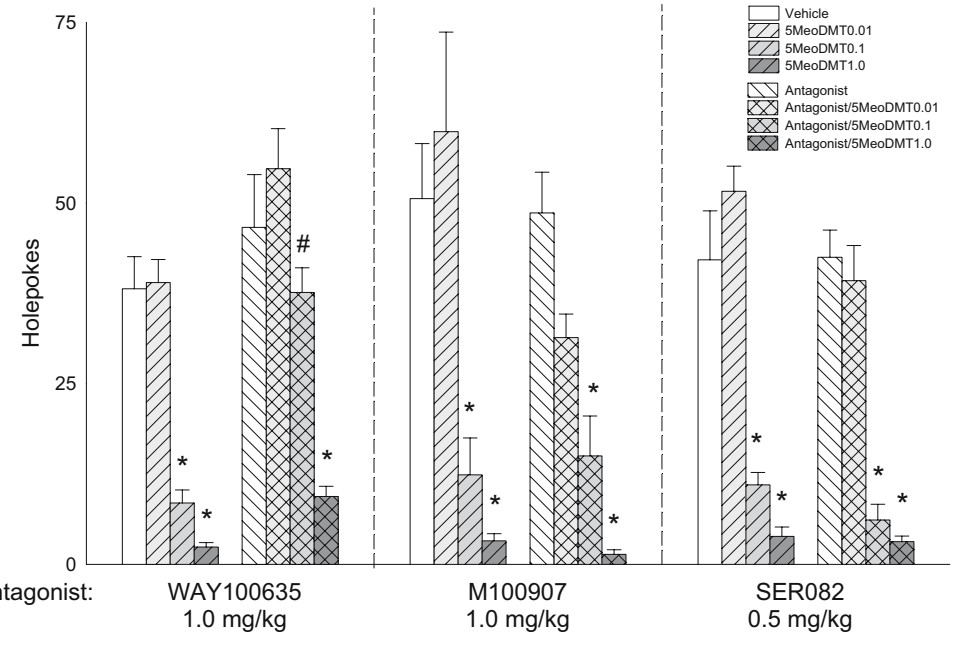

Fig. 2 Antagonist effects on 5-MeO-DMT-induced decreases in investigation. 5-MeO-DMT decreased holepokes, a measure of investigatory activity. *Dashed lines* divide the three separate experiments. In all three experiments both the 0.1- and 1.0-mg/kg doses of 5-MeO-DMT significantly reduced holepokes. Only WAY-100635 pretreatment significantly attenuated the effect of 0.1 mg/kg of 5-MeO-DMT. Data are presented as group means±SEM for the initial 10 min of testing. *$p<0.05$, group is different from its vehicle control group. #$p<0.05$, group is different from its vehicle/5-MeO-DMT group

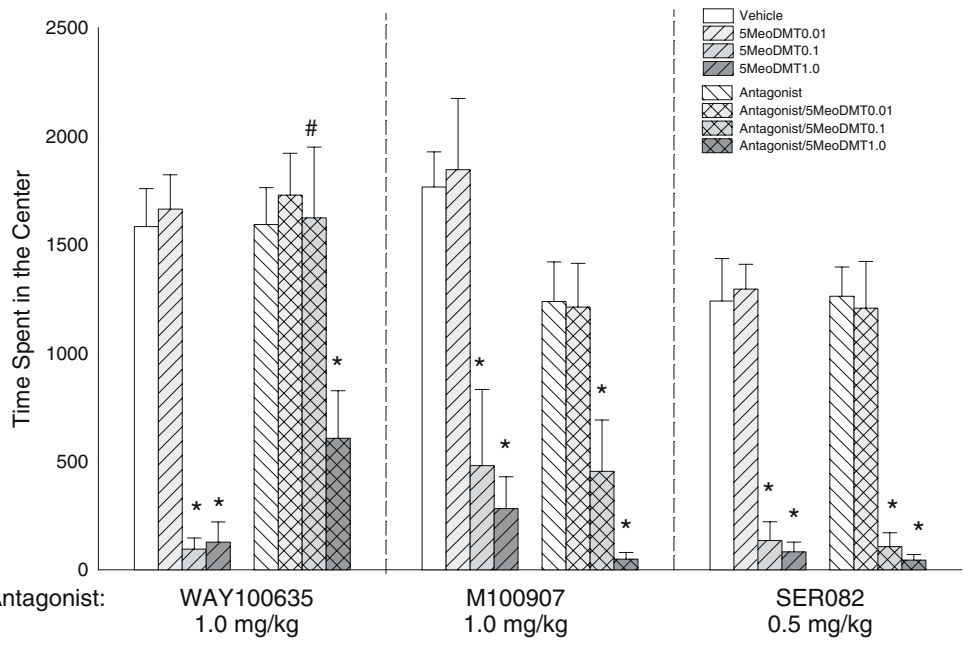

Fig. 3 Antagonist effects on 5-MeO-DMT-induced decreases in center duration. 5-MeO-DMT decreased the time spent in the center of the BPM chamber. *Dashed lines* divide the three separate experiments. In all three experiments, both the 0.1- and 1.0-mg/kg doses of 5-MeO-DMT significantly reduced center duration. Only WAY-100635 pretreatment significantly attenuated the effect of 0.1 mg/kg of 5-MeO-DMT. Data are presented as group means±SEM for the initial 10 min of testing. *$p<0.05$, group is different from its vehicle control group. #$p<0.05$, group is different from its vehicle/5-MeO-DMT group

($p=0.00$) on center duration. There was also a significant interaction of 5-MeO-DMT treatment with time [$F(15,280=4.54$, $p=0.00$]. For the initial 10 min of testing, again, there were significant effects of M100907 pretreatment [$F(1,56)=4.93$, $p=0.03$] and 5-MeO-DMT treatment [$F(3,56)=19.30$, $p=0.00$] on the time spent in the center, but no interaction was found. Specific comparisons confirmed that the 0.1- and 1.0-mg/kg doses of 5-MeO-DMT reduced center duration, but there was no attenuation of these effects by M100907 pretreatment (Fig. 3).

Experiment 3 Sixty-four rats ($n=8$/group) were treated with either vehicle or 0.5 mg/kg SER-082 20 min before injection of either vehicle or 5-MeO-DMT (0.01, 0.1, or 1.0 mg/kg).

Results and discussion There was a significant 5-MeO-DMT treatment effect on crossings [$F(3,56)=16.84$, $p=0.00$] and a three-way interaction of SER-082 pretreatment and 5-MeO-DMT treatment with time [$F(15,280)=2.09$, $p=0.01$]. Analysis of the initial 10 min of testing revealed a significant interaction between SER-082 pretreatment and 5-MeO-DMT treatment [$F(3,56)=3.27$, $p=0.03$]. Specific comparisons revealed that the 0.1- and 1.0-mg/kg doses of 5-MeO-DMT decreased crossings (Fig. 1). Despite the significant interaction, there were no significant differences that would indicate antagonism, although a trend for SER-082 pretreatment to attenuate the effects of 1.0 mg/kg of 5-MeO-DMT may explain the significant interaction (Fig. 1).

With respect to holepokes, there was a significant 5-MeO-DMT treatment effect [$F(3,56)=25.67$, $p=0.00$] and an interaction of 5-MeO-DMT with time [$F(15,280)=1.89$, $p=0.02$]. For the first 10 min of testing, there was a significant effect of 5-MeO-DMT treatment on holepokes [$F(3,56)=72.96$, $p=0.00$], specifically after treatment with 0.1 and 1.0 mg/kg of 5-MeO-DMT (Fig. 2). Thus, while 5-MeO-DMT treatment reduced investigatory activity, SER-082 pretreatment failed to attenuate this effect.

There was a significant effect of 5-MeO-DMT treatment on center duration [$F(3,56)=16.76$, $p=0.00$]. There was also a significant interaction of 5-MeO-DMT treatment with time [$F(15,280)=3.04$, $p=0.00$]. Analysis of the initial 10 min of testing revealed that there was a significant effect of 5-MeO-DMT treatment [$F(3,56)=54.99$, $p=0.00$], but no interaction. Specific comparisons showed that 0.1 and 1.0 mg/kg of 5-MeO-DMT reduced center chamber duration, but this effect was not attenuated by SER-082 pretreatment (Fig. 3).

PPI studies

Experiment 4 Sixty-four rats ($n=8$/group) were treated with either vehicle or 1.0 mg/kg of WAY-100635 20 min before injection of either vehicle or 5-MeO-DMT (0.01, 0.1, or 1.0 mg/kg).

Results and discussion There was a significant overall interaction between WAY-100635 and 5-MeO-DMT [$F(3,56)=5.97$, $p=0.00$] on PPI. As there was no interaction of WAY-100635 or 5-MeO-DMT with block, further analyses collapsed across block. There was a significant interaction between WAY-100635 and 5-MeO-DMT and prepulse intensity [$F(6,112)=2.29$, $p=0.04$]. Thus, further analyses were performed for the individual intensities. There were significant interactions between WAY-100635 and 5-MeO-

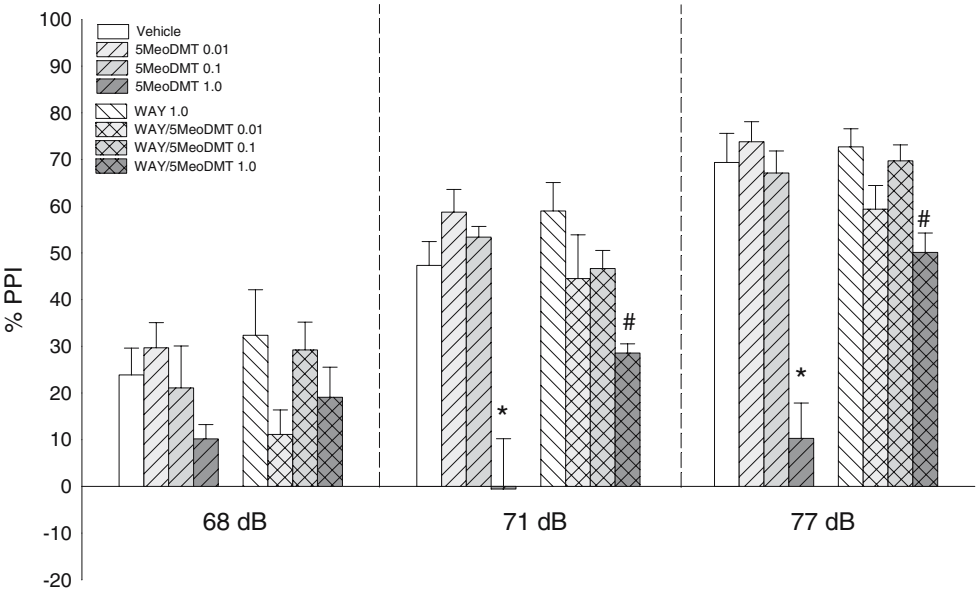

Fig. 4 WAY100635 attenuates 5-MeO-DMT PPI disruption. 5-MeO-DMT treatment significantly disrupted *PPI*. The highest dose of 5-MeO-DMT (1.0 mg/kg) decreased PPI at the 71- and 77-dB intensities. This PPI disruption was significantly attenuated by 1.0 mg/kg of WAY-100635 pretreatment. Data are presented as group means± SEM. *$p<0.05$, group is different from its vehicle control group. #$p<0.05$, group is different from its vehicle/5-MeO-DMT group

DMT for the 71-dB [$F(3,56)=4.81$, $p=0.00$] and 77-dB prepulse intensities [$F(3,56)=10.14$, $p=0.00$]. Specific comparisons revealed that the 1.0-mg/kg dose of 5-MeO-DMT significantly disrupted PPI at both intensities. WAY-100635 pretreatment successfully antagonized these disruptions, as revealed by significant differences between the WAY-100635/5-MeO-DMT 1.0 group and the Vehicle/5-MeO-DMT 1.0 group (Fig. 4). There were no significant effects of either WAY-100635 or 5-MeO-DMT on startle magnitude and no significant interactions (Table 1).

Experiment 5 Sixty-four rats ($n=8$/group) were treated with either vehicle or 1.0 mg/kg of M100907 20 min before injection of either vehicle or 5-MeO-DMT (0.01, 0.1, or 1.0 mg/kg).

Results and discussion There was a significant main effect of 5-MeO-DMT on PPI [$F(3,56)=11.39$, $p=0.00$]. There was also a significant interaction of 5-MeO-DMT with block [$F(3,56)=3.80$, $p=0.02$]. There was no significant interaction between M100907 and 5-MeO-DMT and none between M100907 and 5-MeO-DMT and any other factor (Fig. 5). We did not collapse across intensity, as the previous experiment had demonstrated the dependence of effects on intensity and thus we present the data in a similar way. Similarly, although there was a significant interaction with time for this experiment, examination of the data did not reveal any interaction and thus are presented collapsed across block for simplicity and to accord with the other experiment. There was a significant effect of 5-MeO-DMT alone on startle magnitude [$F(3,56)=2.99$], although none of the specific comparisons reached significance (Table 1).

Table 1 5-MeO-DMT treatment significantly affected startle magnitude only in the M100907 study

Group (pretreatment/treatment)	Startle magnitude
Vehicle/vehicle	364.46±27.26
Vehicle/5-MeO-DMT (0.01 mg/kg)	461.02±49.45
Vehicle/5-MeO-DMT (0.1 mg/kg)	367.03±75.56
Vehicle/5-MeO-DMT (1.0 mg/kg)	426.37±39.86
WAY100635 (1.0 mg/kg)/vehicle	487.86±124.73
WAY100635 (1.0 mg/kg)/5-MeO-DMT (0.01 mg/kg)	329.97±55.47
WAY100635 (1.0 mg/kg)/5-MeO-DMT (0.1 mg/kg)	344.30±41.21
WAY100635 (1.0 mg/kg)/5-MeO-DMT (1.0 mg/kg)	297.75±48.39
Vehicle/vehicle	290.57±54.48
Vehicle/5-MeO-DMT (0.01 mg/kg)	407.62±220.19
Vehicle/5-MeO-DMT (0.1 mg/kg)	421.36±192.99
Vehicle/5-MeO-DMT (1.0 mg/kg)	330.75±61.54
SER-082 (0.5 mg/kg)/vehicle	398.91±64.69
SER-082 (0.5 mg/kg)/5-MeO-DMT (0.01 mg/kg)	553.73±128.01
SER-082 (0.5 mg/kg)/5-MeO-DMT (0.1 mg/kg)	387.03±97.21
SER-082 (0.5 mg/kg)/5-MeO-DMT (1.0 mg/kg)	329.84±41.16
Vehicle/vehicle	256.17±30.34
Vehicle/5-MeO-DMT (0.01 mg/kg)	373.42±73.61
Vehicle/5-MeO-DMT 0.1 mg/kg	365.14±56.22
Vehicle/5-MeO-DMT 1.0 mg/kg	263.71±44.50
M100907 (1.0 mg/kg)/vehicle	408.95±78.18
M100907 (1.0 mg/kg)/5-MeO-DMT (0.01 mg/kg)	438.96±63.03
M100907 (1.0 mg/kg)/5-MeO-DMT (0.1 mg/kg)	326.13±77.38
M100907 (1.0 mg/kg)/5-MeO-DMT (1.0 mg/kg)	190.55±45.88

There was no effect of any antagonist, WAY100635, SER-082, or M100907, on startle reactivity. There was a significant treatment effect of 5-MeO-DMT in the M100907 study, although no specific group was significantly different from another. Data are presented as group means±SEM

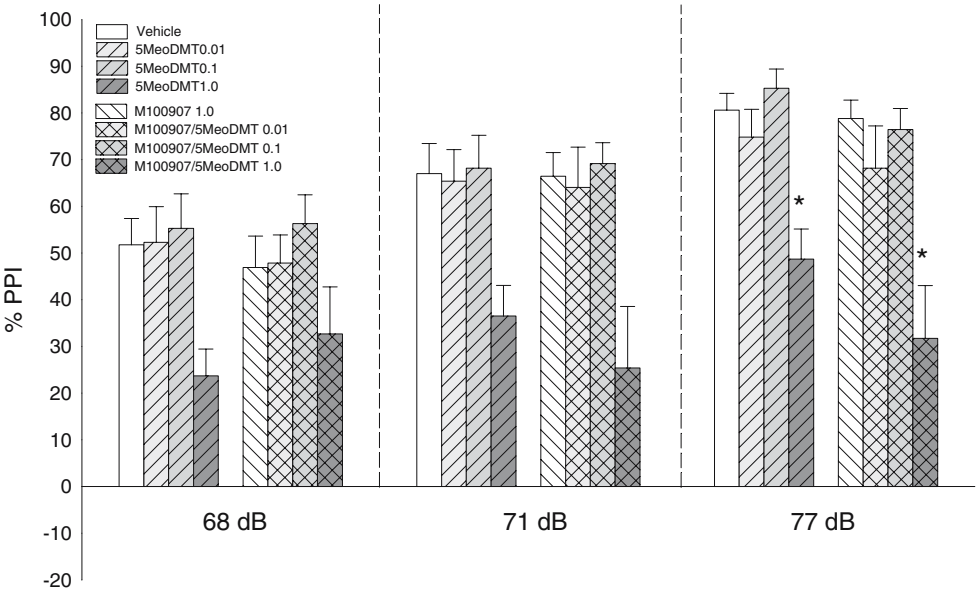

Fig. 5 M100907 fails to attenuate the 5-MeO-DMT PPI disruption. 5-MeO-DMT treatment significantly disrupted *PPI*. The highest dose of 5-MeO-DMT (1.0 mg/kg) decreased PPI at the 77-dB intensity. This PPI disruption was not attenuated by 1.0 mg/kg of M100907 pretreatment at any intensity. Data are presented as group means± SEM. *$p<0.05$, group is different from its vehicle control group

Experiment 6 Sixty-four rats ($n=8$/group) were treated with either vehicle or 0.5 mg/kg SER-082 20 min before injection of either vehicle or 5-MeO-DMT (0.01, 0.1, or 1.0 mg/kg).

Results and discussion There was a significant main effect of 5-MeO-DMT on PPI [$F(3,56)=16.46$, $p=0.00$]. As there was no interaction of SER-082 or 5-MeO-DMT with block, further analyses collapsed across block. There was a three-way interaction between SER-082, 5-MeO-DMT, and intensity [$F(6,112)=2.53$, $p=0.02$], so further analyses were performed for the individual prepulse intensities. There were main effects of 5-MeO-DMT at the 68-dB [$F(3,56)=7.45$, $p=0.00$] and 71-dB [$F(3,56)=11.49$, $p=0.00$] prepulse intensities. There was an interaction between SER-082 and 5-MeO-DMT for the 77-dB intensity [$F(3,56)=3.33$, $p=0.03$]. Specific comparisons demonstrated that the 1.0-mg/kg dose of 5-MeO-DMT reduced PPI at the 77-dB intensity, which was antagonized by SER-082 pretreatment, as revealed by a significant difference between the SER-082/5-MeO-DMT 1.0 group and the Vehicle/5-MeO-DMT 1.0 group (Fig. 6). There was no significant effect of either SER-082 or 5-MeO-DMT on startle magnitude, nor any significant interactions (Table 1).

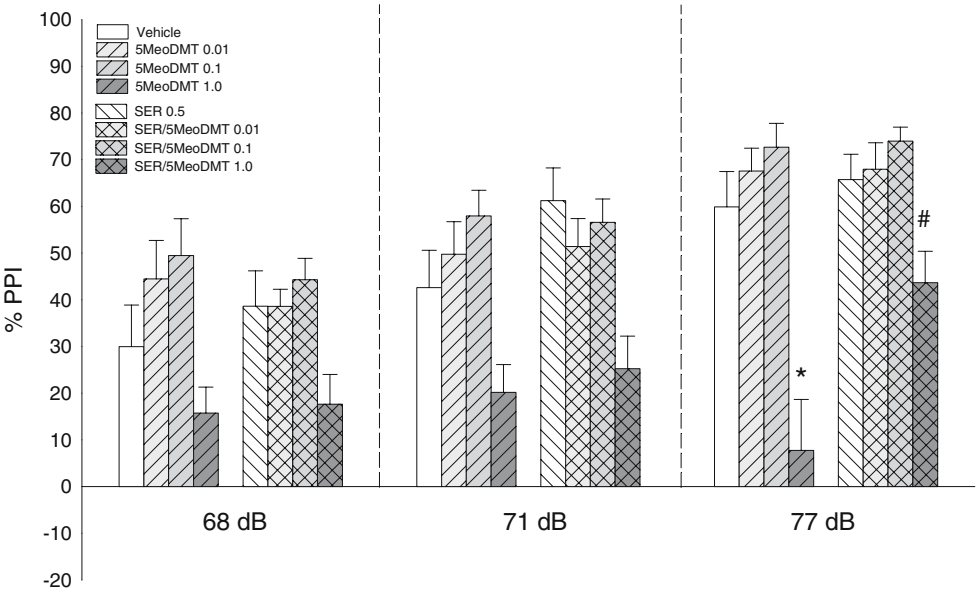

Fig. 6 SER-082 partially attenuates 5-MeO-DMT PPI disruption. 5-MeO-DMT treatment significantly disrupted *PPI*. The highest dose of 5-MeO-DMT (1.0 mg/kg) decreased PPI at the 77-dB intensity. This PPI disruption was significantly attenuated by 0.5 mg/kg of SER-082 pretreatment. Data are presented as group means±SEM. *$p<0.05$, group is different from its vehicle control group. #$p<0.05$, group is different from its vehicle/5-MeO-DMT group

Discussion

In the present studies, the hallucinogen 5-MeO-DMT was found to decrease locomotor activity, investigatory behavior, and center duration and to disrupt PPI of startle in rats. All of these effects of 5-MeO-DMT were antagonized by pretreatment with the 5-HT_{1A} antagonist WAY-100635. In contrast, pretreatment with the 5-HT_{2A} antagonist M100907 failed to attenuate any of these effects, while the 5-HT_{2C} antagonist SER-082 pretreatment only reduced the PPI disruption produced by 5-MeO-DMT.

In the exploratory activity studies, 5-MeO-DMT decreased locomotion, investigation, and center duration. These effects are consistent with previous results demonstrated with other hallucinogens, such as LSD, DOI, and DOM (Adams and Geyer 1982, 1985a,b; Geyer and Krebs 1994; Krebs-Thomson et al. 1998). These effects, when produced by the phenalkylamine hallucinogen DOI, were attributable solely to the activation of 5-HT_{2A} receptors, which accords well with the prevailing view that 5-HT_2 receptors are responsible for hallucinogenic activity (Glennon et al. 1984; Krebs-Thomson et al. 1998; Titeler et al. 1988). When these effects were produced by the indoleamine hallucinogen LSD, however, the pattern was more complicated. The decrease in locomotion produced by LSD was attenuated only by 5-HT_{1A} antagonism, while the decrease in investigation was antagonized only by 5-HT_{2A} antagonism (Krebs-Thomson and Geyer 1996; Krebs-Thomson et al. 1998). The effect of LSD on locomotor patterns was attenuated by 5-HT_{1A}, 5-HT_{2A}, or 5-HT_{2C} antagonism. This pattern was not reproduced by 5-MeO-DMT. Despite their apparent similarities, 5-MeO-DMT behaves somewhat differently than LSD in the BPM paradigm with these antagonists. The reduction in locomotor activity by 5-MeO-DMT was attenuated by 5-HT_{1A} antagonism, as it was with LSD. As with LSD, no other antagonist reduced this locomotor activity decrement produced by 5-MeO-DMT, although there may have been a slight trend with SER-082 pretreatment. The decrease in investigation produced by 5-MeO-DMT was also antagonized by 5-HT_{1A} antagonism, an effect not found with LSD. Neither 5-HT_{2A} nor 5-HT_{2C} antagonism attenuated this effect on investigation. While the effect of LSD on investigation was attributable to 5-HT_{2A} activation, it appears that 5-HT_{1A} receptors play the primary role in the effect of 5-MeO-DMT on investigatory behavior. The decrease in center duration produced by 5-MeO-DMT was also attenuated only by 5-HT_{1A} antagonism. While 5-HT_{1A} receptors do play a role in the effect of LSD on locomotor patterns, both 5-HT_{2A} and 5-HT_{2C} receptors also contribute. In summary, it appears that the effects of the established hallucinogen 5-MeO-DMT in the BPM paradigm are primarily attributable to the activation of 5-HT_{1A} receptors.

This emphasis on 5-HT_{1A} receptors and the lack of evidence for the importance of the 5-HT_{2A} and 5-HT_{2C} receptors is puzzling. The pattern of effects with 5-MeO-DMT appears more similar to that produced by the presumably nonhallucinogenic 5-HT_{1A} agonist 8-OH-DPAT (Krebs-Thomson and Geyer 1996), than to the hallucinogen LSD. On the other hand, we have consistently demonstrated that 5-HT_{1A} receptors do play an important role in the effects of indoleamine hallucinogens in the BPM (Krebs and Geyer 1994; Krebs-Thomson and Geyer 1996, 1998; Krebs-Thomson et al. 1998). Because 5-HT_{1A} agonists do not demonstrate hallucinogenic activity in humans (Gammans et al. 1986) and do not generally substitute for hallucinogens in discriminative stimulus tasks in animals (Cunningham and Appel 1987; Glennon 1986), the potential importance of these receptors in hallucinogenic activity has often been discounted. Our results with LSD, and now with 5-MeO-DMT, support the significant role that 5-HT_{1A} receptors play in the behavioral effects of the indoleamine hallucinogens, although obviously, animal studies cannot determine if 5-HT_{1A} receptors play a role in the expression of "hallucinogenic" effects in humans. Drug discrimination results also support the importance of 5-HT_{1A} receptors to the stimulus control effects of 5-MeO-DMT (Winter et al. 2000). The other important point is that 5-MeO-DMT is not the same as LSD, which is technically an ergot alkaloid. The fact that 5-MeO-DMT did not replicate the behavioral profile produced by LSD provides further evidence for qualitative differences between the two drugs.

The highest dose of 5-MeO-DMT disrupted PPI in all three studies. In the WAY-100635 study, 1.0 mg/kg of 5-MeO-DMT reduced PPI at both the 71- and 77-dB prepulse intensities. In the SER-082 and M100907 studies, the disruption was statistically robust only at the 77-dB prepulse intensity, but similar mean differences were also apparent with the lower intensity prepulses. The PPI disruption induced by 5-MeO-DMT was significantly attenuated by either WAY-100635 or SER-082 pretreatment, but not by M100907. Previous reports have confirmed that stimulation of 5-HT_{1A} receptors disrupts PPI in rats (Rigdon and Weatherspoon 1992; Sipes and Geyer 1995a). In keeping with the former result, previous work showed that even lower doses of WAY-100635 are effective in reducing the effects of LSD on locomotor activity (Krebs-Thomson and Geyer 1996). In contrast, the SER-082 dose that was effective in reducing the effects of 5-MeO-DMT on PPI in the present study was ineffective in altering the PPI-disruptive effect of the hallucinogen DOI in previous work (Sipes and Geyer 1995b). The 1.0-mg/kg of M100907 pretreatment, however, had no effect on the 5-MeO-DMT-induced PPI disruption, despite the fact that both 0.1 and 1.0 mg/kg doses of M100907 were shown to

be effective in blocking the PPI-disruptive effects of DOI (Sipes and Geyer 1995b). The effects of 5-MeO-DMT on PPI did not appear to be confounded by changes in startle reactivity, as 5-MeO-DMT did not affect startle magnitude in either the WAY-100635 or SER-082 studies. In the M100907 study, there was a significant effect of 5-MeO-DMT on startle magnitude, but not at the dose of 5-MeO-DMT that affected PPI. The effects of 5-MeO-DMT on PPI were thus decreased by a 5-HT_{1A} antagonist, WAY-100635, and by a putative 5-HT_{2C} antagonist, SER-082. The 5-HT_{2A} antagonist M100907 had no effect on the PPI-disruptive effect of 5-MeO-DMT. Thus, it appears that the effects of 5-MeO-DMT on PPI are attributable in part to actions at 5-HT_{1A} and 5-HT_{2C} receptors, but not at 5-HT_{2A} receptors.

These results with PPI again highlight the difference between 5-MeO-DMT and LSD, as other researchers have found that only 5-HT_{2A} antagonism, produced by M100907, reduced the PPI deficits produced by a high dose of LSD (Ouagazzal et al. 2001). Neither SER-082 nor WAY-100135 pretreatment antagonized the effects of LSD, although WAY-100135 is not as potent or effective as WAY-100635 and that fact may have influenced the lack of an interaction. Thus, our results with 5-MeO-DMT seem opposite to those obtained by others with LSD (Ouagazzal et al. 2001).

The effects of 5-MeO-DMT on both locomotor activity and PPI demonstrate the importance of 5-HT_{1A} receptors to the effects of the hallucinogen 5-MeO-DMT in these paradigms. While the prevailing view has been that it is solely the activation of 5-HT_2 receptors that is responsible for hallucinogenic drug effects, these results support a role for 5-HT_{1A} receptors in the effects of the indoleamine hallucinogens on locomotor activity and PPI.

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