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Modification of the effects of 5-methoxy-*N*,*N*-dimethyltryptamine on exploratory behavior in rats by monoamine oxidase inhibitors

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Abstract

RATIONALE—The hallucinogenic tea known as *ayahuasca* is made from a combination of psychoactive plants that contribute the active components *N*,*N*-dimethyltryptamine (DMT) and 5-methoxy-DMT (5-MeO-DMT), as well as the monoamine oxidase (MAO) inhibitors (MAOIs) harmine and harmaline for oral activity.

OBJECTIVE—The present study examined the effects of 5-MeO-DMT in combination with MAOIs in rats using the Behavioral Pattern Monitor (BPM), which enables analyses of patterns of locomotor activity and exploration. Interaction studies using the serotonin $(5\text{-HT})_{1A}$ antagonist WAY-100635 (1.0 mg/kg) and the 5-HT_{2A} antagonist MDL 11,939 (1.0 mg/kg) were also performed to assess the respective contributions of these receptors to the behavioral effects of 5-MeO-DMT in MAOI-treated animals.

RESULTS—5-MeO-DMT (0.01, 0.1, and 1.0 mg/kg) decreased locomotor activity and investigatory behavior. In rats pretreated with a behaviorally inactive dose of harmaline (0.1 mg/kg), 1.0 mg/kg 5-MeO-DMT had biphasic effects on locomotor activity, initially reducing locomotion and then increasing activity as time progressed. The ability of harmaline to shift 5-MeO-DMT to a biphasic locomotor pattern was shared by the selective MAO_A inhibitor clorgyline, whereas the selective MAO_B inhibitor (−)-deprenyl was ineffective. The late hyperactivity induced by the combination of 1.0 mg/kg 5-MeO-DMT and 0.3 mg/kg clorgyline was blocked by pretreatment with MDL 11,939. Pretreatment with WAY-100635 failed to attenuate either the early hypoactivity or the late hyperactivity.

CONCLUSIONS—The ability of harmaline to modify the behavioral effects of 5-MeO-DMT is mediated by inhibition of MAO_A. Further, 5-HT_{2A} receptors are responsible for the late hyperactivity induced by 5-MeO-DMT in the presence of MAO_A inhibitors.

Keywords

Ayahuasca; hallucinogen; serotonin; 5-methoxydimethyltryptamine; harmaline; MAOI

Ayahuasca (meaning “vine of the souls” in the Native American language Quechua) is a potent hallucinogenic beverage used by indigenous groups throughout the Amazon basin of South America. This beverage has been used since antiquity to diagnose and cure disease, induce mystical and spiritual states, and to produce euphoria and inebriation (Dobkin de Rios 1972; Schultes and Hofmann 1980). Modern Brazilian syncretic religious groups such as *Santo*

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DISCLOSURE/CONFLICT OF INTEREST
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Daime, *Barquinha*, and *União do Vegetal* (UDV) have adopted the use of ayahuasca as a sacrament, a practice that has spread to Europe and North America. A recent U.S. Supreme Court ruling affirmed the right of members of a UDV branch in New Mexico to import and ingest the ayahuasca sacrament (Anonymous 2006).

Ayahuasca is an infusion or decoction prepared from the jungle liana *Banisteriopsis caapi* together with a number of admixture plants, most frequently *Psychotria viridis* or *Diplopterys cabrerana* (Schultes and Hofmann 1980; McKenna et al. 1984; Schultes and Raffauf 1990). The bark of *B. caapi* contributes β-carbolines such as harmaline and harmine (Rivier and Lindgren 1972; McKenna et al. 1984), which are reversible inhibitors of monoamine oxidase-A (MAO_A) (Buckholtz and Boggan 1977; Glover et al. 1982; Kim et al. 1997). The leaves of the admixture plants, which are required for the psychoactive effects of ayahuasca, contain the hallucinogens *N*,*N*-dimethyltryptamine (DMT) and 5-methoxy-DMT (5-MeO-DMT) (Agurell et al. 1968; Rivier and Lindgren 1972; McKenna et al. 1984). DMT is active by parenteral administration or if smoked (Strassman et al. 1994; Shulgin and Shulgin 1997), but is inactive orally due to substantial first-pass metabolism (Szára 1957; Turner and Merlis 1959). Agurell et al. (1968) first proposed that a specific interaction between β-carbolines and DMT contributes to the oral pharmacological activity of ayahuasca. Indeed, it has been confirmed that DMT and 5-MeO-DMT are orally active when administered in combination with harmaline or harmine (Shulgin and Shulgin 1997; Ott 1999).

Classical hallucinogenic drugs belong to two chemical classes: indoleamines, including (+)-lysergic acid diethylamide (LSD) and DMT; and phenalkylamines, such as mescaline and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM). Indoleamine hallucinogens bind with high affinity to several 5-HT recognition sites including 5-HT_{1A} and 5-HT_2 receptors (Deliganis et al. 1991; McKenna et al. 1990), whereas phenalkylamine hallucinogens are relatively selective for 5-HT_2 receptors (Pierce and Peroutka 1989; Titeler et al. 1988). Considerable evidence indicates that the characteristic effects of hallucinogens are mediated by activation of 5-HT_{2A} receptors. 5-HT_{2A} receptor affinity is strongly correlated with hallucinogenic potency in humans and behavioral activity in animals (Glennon et al. 1984; Titeler et al. 1988; Sadzot et al. 1989). Conversely, selective 5-HT_{1A} agonists are not hallucinogenic in humans and are inactive in animal models predictive of hallucinogenic activity (Koek and Colpaert 1989). Nonetheless, evidence has accumulated demonstrating that indoleamine hallucinogens can induce behavioral effects via 5-HT_{1A} receptors (Li et al. 2007; Krebs-Thomson et al. 2006; Winter et al. 2000; Lucki et al. 1984).

This laboratory has examined the effects of a number of hallucinogens and other pharmacological agents in the Behavioral Pattern Monitor (BPM). The BPM combines the features of activity and holeboard chambers to assess both the quantity and several aspects of the quality of unconditioned locomotor and investigatory activity in rats (Geyer 1990). Hallucinogens produce characteristic effects in the BPM. When tested in a novel environment, members of both the phenalkylamine and indoleamine classes of hallucinogens decrease locomotor and investigatory responding and increase avoidance of central areas of the BPM chamber (Geyer et al. 1979; Adams and Geyer 1985a; Wing et al. 1990; Mittman and Geyer 1991; Krebs-Thomson et al. 2006). LSD also decreases investigatory behavior and center entries (Adams and Geyer 1985b), but it has biphasic effects on locomotor behavior, initially suppressing locomotor activity and subsequently increasing activity as time progresses (Mittman and Geyer 1991). Most effects of phenalkylamine hallucinogens in the BPM are blocked by 5-HT_{2A} but not 5-HT_{2C} selective antagonist treatment (Krebs-Thomson et al. 1998), and are likely solely attributable to activation of 5-HT_{2A} receptors. The mechanistic basis for effects of indoleamine hallucinogens in the BPM is much more complex, and appears to involve 5-HT_1 and 5-HT_2 receptor activation (Krebs-Thomson and Geyer 1996; Krebs-Thomson et al. 2006; Mittman and Geyer 1991).

The goal of the present investigation was to characterize the behavioral effects induced by parenteral administration of 5-MeO-DMT alone and in combination with harmaline, using the BPM paradigm. Ayahuasca typically contains DMT; however, DMT is a difficult drug to use in extended animal studies because it has a very short duration of action. Indeed, previous studies conducted in this laboratory demonstrated that DMT fails to alter locomotor activity when tested in the BPM (Adams and Geyer 1985a). The related compound 5-MeO-DMT has similar pharmacology to DMT (Glennon et al. 1982), and is more practical to use in animal studies because it is longer acting (Krebs-Thomson et al. 2006). Additionally, there is evidence that preparations containing 5-MeO-DMT and MAO inhibitors are being used recreationally for their hallucinogenic properties (Brush et al. 2004; Sklerov et al. 2005). Hence, we used the combination of harmaline and 5-MeO-DMT as an approximation of ayahuasca. The primary pathway for metabolism of 5-MeO-DMT is deamination by MAO_A (Agurell et al. 1969; Squires 1975; Suzuki et al. 1981; Sitaram et al. 1987b). Thus, the hypothesis was tested that harmaline pretreatment will produce a shift in the dose-response or duration of action of 5-MeO-DMT in rats. We also explored whether selective MAO inhibitors produce behavioral interactions with 5-MeO-DMT, and assessed the respective contributions of $5\text{-}HT_{1A}$ and $5\text{-}HT_{2A}$ receptors to these effects.

MATERIALS AND METHODS

Animals

Male Sprague–Dawley rats (Harlan Industries, Indianapolis, IN, USA) (initial weight 250 to 275 g) were housed in pairs in a temperature and humidity controlled vivarium under a 12 h: 12 h reverse light-dark cycle (lights off at 0700 hours). Food and water were available *ad libitum*. Animals were acclimatized for approximately 1 week after arrival prior to behavioral testing and maintained in American Association for Accreditation of Laboratory Animal Care approved facilities that meet all Federal and State guidelines. Procedures were approved by the University of California San Diego (UCSD) institutional animal care and use committee. Principles of laboratory animal care were followed as well as specific laws of the United States.

Apparatus

Behavior was measured in the BPM, a 30.5 × 61.0 × 28.0 cm black Plexiglas chamber equipped with 2.5 cm holes in the walls and floor (for details, see Geyer et al. 1986). Photocells in each hole detected investigatory nosepokes (holepokes). Rearings were detected by continuity between the metal floor of the chamber and a touchplate located 15.2 cm above the floor. A 4 × 8 grid of infrared photobeams was used to detect the animal's position in an X–Y plane. A computer continuously monitored the status of the photobeams and the touchplate and stored the data for subsequent off-line analysis.

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 brought to the testing room and allowed to sit for 60 min before receiving injections. Injections were administered under red lights in the testing room. Animals were tested during the dark phase in darkness. Each animal was tested twice in the BPM, with a two-week washout period between sessions. Drug doses and pre-injection times were chosen based on preliminary dose-finding experiments (data not shown) or based on the results of previously published studies. Unless otherwise noted, animals were placed in the BPM chambers 10 min after 5-MeO-DMT treatment, and behavior monitored for 60 min.

In experiment 1, rats (*n*=8, 64 total) were treated with harmaline (0 or 0.1 mg/kg) 20 min before administration of 5-MeO-DMT (0, 0.01, 0.1, or 1.0 mg/kg). In experiment 2, rats (*n*=7–8, 46 total) were treated with the selective MAO_A inhibitor clorgyline (0 or 0.3 mg/kg) 20 min before administration of 5-MeO-DMT (0, 0.3 or 1.0 mg/kg). In experiment 3, rats, (*n*=8, 48 total) were treated with the selective MAO_B inhibitor (−)-deprenyl (0 or 1.0 mg/kg) 20 min before administration of 5-MeO-DMT (0, 0.3 or 1.0 mg/kg). In experiment 4, rats (*n*=6–8, 60 total) were treated with harmaline (0 or 0.1 mg/kg) 20 min before administration of DOM (0, 0.1, 0.3, 1.0 mg/kg). In experiment 5, rats (*n*=7–8, 30 total) were treated with the selective 5-HT_{1A} antagonist WAY-100635 (0 or 1.0 mg/kg) 20 min before administration of vehicle or 1.0 mg/kg 5-MeO-DMT. All animals injected with 5-MeO-DMT were pretreated (20 min) with 0.3 mg/kg clorgyline. In experiment 6, rats (*n*=7–8, 31 total) were treated with vehicle or 0.3 mg/kg of the selective 5-HT_{2A} antagonist MDL 11,939 20 min before vehicle or 1.0 mg/kg 5-MeO-DMT. All animals injected with 5-MeO-DMT were pretreated (20 min) with 0.3 mg/kg clorgyline. In experiment 7, two groups of 16 rats each were used. Group 1 was injected twice with vehicle, with a 20-min interval between injections. Group 2 was injected with 0.3 mg/kg clorgyline 20 min before injection of 1.0 mg/kg 5-MeO-DMT. Rats were assigned randomly, half of the animals of each group being placed in the BPM chamber 10 min after receiving 5-MeO-DMT or the second vehicle injection (CLODMT-10″, VEH-10″, respectively) and the other half 40 min after receiving 5-MeO-DMT or the second vehicle injection (CLODMT-40″, VEH-40″, respectively). Finally, in experiment 8, two groups of 8 rats each were tested in the BPM for 60 min. After removal from the chambers, the first group of animals was injected twice with vehicle, with a 20-min interval between injections. The second group was injected with clorgyline (0.3 mg/kg) 20 min before injection of 5-MeO-DMT (1.0 mg/kg). Animals were then returned to the same BPM chamber 40 min after receiving 5-MeO-DMT or the second vehicle injection, and tested for 60 min.

Analysis

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 (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 (center duration) was quantified by the time spent in the center. The number of holepokes and rearings were calculated. Analysis of the spatial structure of rat locomotor paths was performed by calculating a descriptive statistic, spatial d. The statistic d is based conceptually on fractal geometry and calculated using scaling arguments, as described in detail by Paulus and Geyer (1991). Changes in d reflect smoother (decreases in d) or rougher (increases in d) locomotor paths. Data were examined in 10-min and 30-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.

Drugs

Drugs used were: *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide maleate (WAY-100635), 5-MeO-DMT, *N*-methyl-*N*-propargyl-3-(2,4-dichlorophenoxy)-propylamine HCl (clorgyline), *R*(−)-deprenyl HCl (Sigma-Aldrich, St. Louis, MO, USA); α-phenyl-1-(2-phenylethyl)-4-piperidinemethanol (MDL 11,939; Tocris Bioscience, Ellisville, MO); harmaline HCl dihydrate (INDOFINE Chemical Company, Hillsborough, NJ, USA); and DOM HCl (National Institute on Drug Abuse, Rockville, MD, USA). Drug doses are expressed as the salt form of the drug with the exception of 5-MeO-DMT and MDL 11,939 which refer to the freebase. 5-MeO-DMT,

harmaline, and DOM were dissolved in nitrogen-purged isotonic saline. MDL 11,939 was dissolved in saline (pH 5.0) containing 0.75% Tween 80. All other drugs were dissolved in isotonic saline. All drugs were administered subcutaneously in a volume of 1 ml/kg.

RESULTS

Experiment 1

Pretreatment with 0.1 mg/kg harmaline alone had no effect on crossings, a measure of horizontal locomotor activity. 5-MeO-DMT treatment had a significant effect on crossings [$F(3,56)=27.17$, $P<0.0001$], and interacted with time [$F(15,280)=41.48$, $P<0.0001$]. Post-hoc analysis demonstrated that the 0.1 and 1.0 mg/kg doses of 5-MeO-DMT significantly reduced crossings during the first 30 min of the session. Interestingly, there was an interaction between harmaline pretreatment and 5-MeO-DMT treatment for crossings [$F(3,56)=3.50$, $P=0.02$]. The interaction between harmaline and 5-MeO-DMT was dose-dependent and biphasic, producing an interaction of pretreatment and treatment with time [$F(15,280)=3.04$, $P=0.0001$]. The combination of harmaline and 0.1 or 1.0 mg/kg 5-MeO-DMT *reduced* crossings during the first 30 min of the 1-h test session. The initial decrease in locomotor activity induced by 5-MeO-DMT in animals pretreated with harmaline was qualitatively similar to that induced by 5-MeO-DMT in vehicle-pretreated animals. Conversely, in harmaline-pretreated animals, 1.0 mg/kg 5-MeO-DMT *increased* crossings during the second 30 min (Fig. 1a). A delayed increase in locomotor activity was never observed when 5-MeO-DMT was administered alone, even at dosages greater than 1.0 mg/kg (Halberstadt and Geyer, unpublished observations), and was not observed when the 0.01- and 0.1-mg/kg doses of 5-MeO-DMT were administered to harmaline-pretreated animals.

There was no effect of harmaline pretreatment on spatial d, a measure of the complexity of locomotor paths. 5-MeO-DMT treatment altered spatial d [$F(3,55)=8.17$, $P=0.0001$], although post hoc analysis failed to confirm this effect for any specific 30-min time block. Finally, there was a nonsignificant interaction between harmaline pretreatment and 5-MeO-DMT treatment for spatial d [$F(3,55)=2.50$, $P=0.069$]. Specific comparisons revealed that compared to vehicle-treated animals the combination of 0.1 mg/kg harmaline pretreatment and 1.0 mg/kg 5-MeO-DMT treatment reduced spatial d during the second 30 min of the session (see Fig. 1b). This effect did not occur when lower doses of 5-MeO-DMT were administered to harmaline-pretreated animals.

As illustrated in Fig. 1c–e, treatment with 5-MeO-DMT produced dose-dependent decreases in rearings [$F(3,56)=42.43$, $P<0.0001$], holepokes [$F(3,56)=59.31$, $P<0.0001$], and center duration [$F(3,56)=5.34$, $P<0.003$]. However, there was no interaction between harmaline pretreatment and 5-MeO-DMT treatment for any of these behavioral measures. Based on these findings, it appears that the effects of 5-MeO-DMT on crossings and spatial d were the only behavioral measures that are altered by harmaline pretreatment.

Experiment 2

In confirmation of the primary hypothesis, there was an interaction between clorgyline pretreatment and 5-MeO-DMT treatment [$F(2,40)=7.83$, $P<0.002$] and a pretreatment–drug–time interaction [$F(10,200)=6.67$, $P<0.0001$]. Indeed, in animals pretreated with 0.3 mg/kg clorgyline, 1.0 mg/kg 5-MeO-DMT altered crossings in a biphasic manner, reducing crossings during the first 30 min of the session and then increasing crossings during the second 30 min (Fig. 2). By contrast, the only effect that 0.3 mg/kg 5-MeO-DMT had on locomotion in clorgyline-pretreated animals was a reduction of crossings during the first 30 min of the session. In addition, the clorgyline pretreatment [$F(1,40)=5.55$, $P<0.03$] and the 5-MeO-DMT treatment [$F(2,40)=6.14$, $P<0.005$] had significant main effects on crossings in addition to

interactions between pretreatment and time [$F(5,200)=8.36$, $P<0.0001$] and treatment with time [$F(10,200)=23.37$, $P<0.0001$]. Specific comparisons demonstrated that the 0.3- and 1.0-mg/kg doses of 5-MeO-DMT reduced crossings during the first 30 min of the session.

Pretreatment with clorgyline had no effect on spatial d. Treatment with 5-MeO-DMT had a significant effect on spatial d [$F(2,40)=3.84$, $P<0.03$]. However, post hoc analysis failed to reveal any 30-min time block during which either 0.3 or 1.0 mg/kg 5-MeO-DMT significantly reduced spatial d. There was no interaction between clorgyline pretreatment and 5-MeO-DMT treatment for spatial d.

Experiment 3

As expected, 5-MeO-DMT treatment reduced crossings [$F(2,40)=31.08$, $P<0.0001$] and spatial d [$F(2,40)=4.53$, $P<0.02$]. However, there was no interaction between (−)-deprenyl pretreatment and 5-MeO-DMT treatment for either of these behavioral measures (data not shown). Spatial d and crossings were unaffected by (−)-deprenyl pretreatment.

Experiment 4

The 0.3 and 1.0 mg/kg doses of DOM reduced crossings [$F(3,52)=34.23$, $P<0.0001$]. DOM had no effect on spatial d. There was no interaction between harmaline pretreatment and DOM treatment for either of these behavioral measures (data not shown).

Experiment 5

As expected, the combination of 0.3 mg/kg clorgyline and 1.0 mg/kg 5-MeO-DMT had a biphasic effect on crossings, resulting in a treatment by time interaction [$F(5,130)=84.03$, $P<0.0001$]. The clorgyline–5-MeO-DMT combination reduced crossings during the first 30 min of the session and increased crossings during the second 30 min of the session (Fig. 3a). WAY-100635 treatment failed to significantly attenuate either the initial decrease in crossings or the delayed increase in crossings induced by clorgyline–5-MeO-DMT treatment. There was a significant effect of WAY-100635 pretreatment with time for crossings [$F(5,130)=3.51$, $P<0.0001$], but post hoc analysis failed to confirm this effect for any specific time block.

Clorgyline–5-MeO-DMT treatment interacted with test time for spatial d [$F(1,26)=12.33$, $P<0.002$]. However, there was no significant interaction between WAY-100635 pretreatment and clorgyline–5-MeO-DMT on spatial d.

Experiment 6

For the crossings measure, there was a three-way interaction between MDL 11,939 pretreatment, clorgyline–5-MeO-DMT treatment, and time [$F(5,135)=9.60$, $P<0.0001$]. As shown in Fig. 3b, MDL 11,939 pretreatment did not alter the initial decrease in crossings, but did antagonize the delayed increase in crossings induced by clorgyline–5-MeO-DMT. In addition, there was an interaction of MDL 11,939 pretreatment with time for crossings [$F(5,135)=8.24$, $P<0.0001$], although post hoc analysis failed to confirm this effect for any specific time block. As in previous studies, the combination of 0.3 mg/kg clorgyline and 1.0 mg/kg 5-MeO-DMT had a biphasic effect on crossings, resulting in an interaction of treatment with time [$F(5,135)=50.39$, $P<0.0001$].

As for spatial d, there was a three-way interaction between MDL 11,939 pretreatment, clorgyline–5-MeO-DMT treatment, and time [$F(1,28)=16.45$, $P=0.0004$]. Specific comparisons revealed that the reduction of spatial d produced by clorgyline–5-MeO-DMT was attenuated by pretreatment with MDL 11,939 (Fig. 3c). There was no main effect of MDL 11,939 on spatial d. The clorgyline–5-MeO-DMT combination decreased spatial d during the

second half-hour of testing, leading to a treatment by time interaction [$F(1,28)=16.45$, $P=0.0004$].

Experiment 7

Increasing the time interval between drug treatment and placement of animals in the BPM chamber (10 min vs. 40 min) altered the effect of drug treatment on crossings, as demonstrated by a three-way interaction between time interval and treatment with time [$F(5,135)=34.30$, $P<0.0001$]. As expected, CLODMT-10″ had a biphasic effect on locomotor activity, reducing crossings during the first 30 min of the session and increasing crossings during the second 30 min (Fig. 4) [treatment by time interaction: $F(5,135)=30.32$, $P<0.0001$]. In contrast, CLODMT-40″ increased crossings during the second and third 10-min time blocks, but did not alter the frequency of crossings during the remainder of the session (Fig. 4). Thus, when the interval between drug treatment and placement of the animals into the BPM chambers is increased by 30 min, the time period during which the locomotor hyperactivity phase is observed was shifted from the second 30 min to the first 30 min of testing (see Fig. 4).

For spatial d, increasing the time interval between CLODMT treatment and placement of animals in the BPM chamber altered the effect of drug treatment, as demonstrated by the three-way interaction between time interval, treatment, and time [$F(1,27)=9.18$, $P<0.01$]. As expected, there was an interaction of CLODMT-10″ treatment with time [$F(1,27)=21.67$, $P<0.0001$]. Specific comparisons revealed that CLODMT-10″ increased spatial d during the first 30 min of the session and decreased spatial d during the second 30 min. CLODMT-40″ had no significant effect on spatial d during either of the 30-min time blocks.

Experiment 8

Treatment with a combination of 0.3 mg/kg clorgyline and 1.0 mg/kg 5-MeO-DMT had no significant effect on crossings when tested in animals previously exposed to the BPM chambers (data not shown). As was found with non-habituated animals, clorgyline–5-MeO-DMT had no effect on spatial d when animals previously exposed to the BPM chambers were tested 40 min after drug treatment.

DISCUSSION

This study demonstrates that 5-MeO-DMT has biphasic effects on locomotor activity in rats pretreated with harmaline, producing an initial reduction in locomotion followed by an increase in activity as time progresses. This biphasic alteration of locomotion is a novel behavioral profile that was not reproduced by either drug alone. The biphasic locomotor pattern was also observed when 5-MeO-DMT was administered in combination with the selective MAO_A inhibitor clorgyline, but did not occur when 5-MeO-DMT was combined with the selective MAO_B inhibitor (−)-deprenyl. Conversely, there was no interaction between harmaline pretreatment and the selective 5-$HT_{2A/2C}$ agonist DOM. The delayed hyperactivity produced by 5-MeO-DMT in clorgyline-pretreated animals was completely antagonized by the 5-HT_{2A} antagonist MDL 11,939. By contrast, the 5-HT_{1A} antagonist WAY-100635 had no effect on either the initial hypoactivity or the delayed hyperactivity produced by the clorgyline–5-MeO-DMT combination.

Harmaline is a competitive, reversible inhibitor of MAO that is highly selective for MAO_A over MAO_B (Buckholtz and Boggan 1977; Glover et al. 1982; Kim et al., 1997). Although harmaline interacts with a number of recognition sites, the dose of harmaline used in this investigation is very low (Robertson 1980) and therefore likely to be relatively selective for MAO_A. The ability of harmaline pretreatment to transform the effect of 5-MeO-DMT in the BPM to a biphasic locomotor profile is shared by both the irreversible MAO_A-selective

inhibitor clorgyline and the irreversible non-selective MAO inhibitor pargyline (Halberstadt and Geyer, unpublished observations). By contrast, the effect of 5-MeO-DMT on crossings was unaltered in animals pretreated with the irreversible MAO_B-selective inhibitor (−)-deprenyl. These findings argue that MAO_A inhibition by harmaline is responsible for the interaction with 5-MeO-DMT.

Pretreatment with the 5-HT_{1A} antagonist WAY-100635 failed to attenuate either the immediate decrease in activity or the late hyperactivity that occurred in response to clorgyline–5-MeO-DMT, suggesting that 5-HT_{1A} receptors are not crucial for these behavioral effects. Although the selectivity of WAY-100635 for 5-HT_{1A} receptors has recently been called into question by the finding that it acts as an agonist at D_4 receptors (Chemel et al. 2006), this observation does not alter our conclusion that the increase in activity induced by combination of clorgyline and 5-MeO-DMT is not mediated by 5-HT_{1A} receptors. We also tested whether the effects of clorgyline–5-MeO-DMT in the BPM paradigm are altered by pretreatment with MDL 11,939, a selective 5-HT_{2A} antagonist. MDL 11,939 displays 295-fold higher affinity for 5-HT_{2A} receptors (K_i = 2.89 nM) than for 5-HT_{2C} receptors (K_i = 853.6 nM), and low affinity for non-5-HT_2 receptors (Pehek et al. 2006). The fact that MDL 11,939 completely antagonized the late hyperactivity produced in response to 5-MeO-DMT in clorgyline-pretreated animals strongly indicates that 5-HT_{2A} receptors are responsible for this effect. Conversely, MDL 11,939 had no significant effect on the initial suppression of crossings by clorgyline–5-MeO-DMT.

As shown previously (Wing et al. 1990; Krebs-Thomson et al. 2006), the effects of 5-MeO-DMT alone in the BPM are of short duration and are not mediated by 5-HT_{2A} receptors. Conversely, in animals pretreated with a MAO_A inhibitor, the action of 5-MeO-DMT is prolonged and involves activation of 5-HT_{2A} receptors. The initial effects of LSD in the BPM resemble those produced by 5-MeO-DMT, since LSD produces an immediate decrease in crossings that is blocked by pretreatment with WAY-100635 (Krebs-Thomson and Geyer 1996). However, as time in the BPM chamber progresses, the initial suppression of crossings induced by LSD gives way to an increase in crossings (Mittman and Geyer 1991). These experiments demonstrate that inhibition of MAO_A alters the behavioral profile of 5-MeO-DMT, shifting it to a biphasic, LSD-like locomotor profile. Significantly, the ability of both LSD (Mittman and Geyer 1991) and clorgyline–5-MeO-DMT to increase locomotor activity is blocked by 5-HT_{2A} antagonists. The finding that activation of 5-HT_{2A} receptors can lead to an increase in locomotor activity is a novel finding; with the exception of LSD, all other 5-HT_{2A} agonists (hallucinogens) examined in the BPM have produced decreases in locomotor activity (Geyer et al. 1979; Adams and Geyer 1985a; Wing et al. 1990; Mittman and Geyer 1991; Krebs-Thomson and Geyer 1996). The decrease in locomotion induced by hallucinogens is significantly reduced in a familiar environment, suggesting this effect involves potentiation of the neophobia exhibited by rats in a novel environment (Adams and Geyer 1985a,b; Wing et al. 1990). When animals treated with clorgyline–5-MeO-DMT were tested in a familiar environment, no increase in locomotor activity was observed. This finding indicates that the 5-HT_{2A}-mediated locomotor effects induced by clorgyline–5-MeO-DMT are also dependent on the novelty of the testing environment. Therefore, it appears that the hyperactivity induced by 5-MeO-DMT when combined with a MAO_A inhibitor is consistent with 5-HT_{2A} activation.

It is likely that the pharmacokinetics of 5-MeO-DMT is altered in animals pretreated with harmaline or clorgyline. In rats, the major pathway for metabolism of 5-MeO-DMT is oxidative deamination to 5-methoxyindoleacetic acid (Agurell et al. 1969; Sitaram et al. 1987b). *In vitro* (Suzuki et al. 1981) and *in vivo* (Squires 1975) experiments have demonstrated that deamination of 5-MeO-DMT is blocked by clorgyline but not (−)-deprenyl, indicating that 5-MeO-DMT is a substrate for MAO_A but not for MAO_B. Given that clorgyline but not (−)-deprenyl alters the behavioral profile of 5-MeO-DMT, it is noteworthy that the former but not the latter drug is also capable of blocking the metabolism of 5-MeO-DMT. Blockade of 5-

MeO-DMT metabolism by MAO_A inhibition may contribute to the alteration of the behavioral effects of this agent in animals pretreated with harmaline or clorgyline. Indeed, it has been demonstrated that the duration of the behavioral syndrome evoked by 5-MeO-DMT in rats is prolonged by pretreatment with pargyline (Ahlborg et al. 1968; Ortman et al. 1980). These observations are consistent with the finding that the persistence of 5-MeO-DMT in rat brain is markedly prolonged in animals pretreated with the nonselective MAO inhibitor iproniazid (Sitaram et al. 1987a).

The time-course study (Experiment 7) demonstrates that the temporal distribution of the effects of the clorgyline–5-MeO-DMT combination on locomotor activity is dependent upon the interval between drug injection and placement of the animals into the BPM chambers. Previous studies have shown that the effects of certain drugs in the BPM paradigm, including LSD and selective 5-HT_{1A} agonists, are not dependent on the time delay between injection and testing (Adams and Geyer 1982; Mittman and Geyer 1989). The finding with clorgyline–5-MeO-DMT indicates that the biphasic locomotor effect of this drug combination reflects distinct temporal phases of drug action, as opposed to an interaction between the drug and the amount of time spent in the chamber during the test session. One possible interpretation of the time-course-dependent nature of the effects of 5-MeO-DMT in clorgyline-pretreated animals is that the late hyperactivity is a consequence of reduced brain clearance of 5-MeO-DMT, leading to prolonged occupation of central 5-HT_{2A} receptors. However, it does not appear that this explanation is sufficient to account for the late hyperactivity induced by clorgyline–5-MeO-DMT because other long-acting 5-HT_{2A} agonists, including DOM (Adams and Geyer 1985a) and DOI (Wing at al. 1990), produce only decreases in locomotor activity. Since DOM has a relatively delayed onset and an extended duration-of-action relative to other hallucinogens (Fiorella et al. 1995), it is possible that the duration of the BPM test session (i.e., ending 70 min after drug treatment) may not have been sufficient to detect DOM-induced hyperactivity. However, the fact that brain levels of (−)-DOM peak between 15 and 30 min after administration to rats (Eckler et al. 2001) suggests that any DOM-induced hyperactivity should be detectable during a 60-min test session. The results obtained with DOM and DOI indicate that prolonged occupation of 5-HT_{2A} receptors by clorgyline–5-MeO-DMT is likely insufficient to fully account for the late hyperactivity induced by that drug combination.

Pretreatment with harmaline failed to alter the behavioral profile of the selective 5-$HT_{2A/2C}$ agonist DOM. The fact that oxidative deamination represents only a minor pathway for DOM metabolism (Ho et al. 1971; Matin et al. 1974; Weinkam et al. 1976; Zweig and Castagnoli 1977) is consistent with the lack of an interaction between harmaline pretreatment and DOM. However, the existence of a purely metabolic interaction between 5-MeO-DMT and MAO_A inhibition does not explain why the behavioral profile associated with 5-MeO-DMT-induced 5-HT_{2A} receptor activation is shifted from hypoactivity to hyperactivity in the presence of harmaline or clorgyline. Alternatively, 5-HT_{2A} receptor activation by 5-MeO-DMT may be necessary but not sufficient to produce a behavioral interaction with MAO_A inhibitors. Binding of 5-MeO-DMT to multiple 5-HT receptor subtypes may be required for this interaction; in addition to 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, 5- MeO-DMT also has high affinity for 5-HT_{1B} (Offord et al. 1988), 5-HT_6 (Monsma et al. 1993), and 5-HT_7 (Shen et al. 1993) sites. 5-MeO-DMT binds to the serotonin (5-HT) transporter with micromolar affinity (Adkins et al. 2001), and blocks the re-uptake of 5-HT (Nagai et al. 2007; Berge et al. 1983). Indeed, behavioral evidence suggests that the pharmacology of this compound is substantially more complex than that of DOM (Winter et al. 2000; Lucki et al. 1984).

The fact that the locomotor effects of 5-MeO-DMT in MAO_A inhibitor-pretreated animals are similar to those of LSD may offer some insight into the nature of the interaction between the former two agents. The pharmacology of LSD is complex—LSD is a nonselective serotonin receptor agonist, but also binds to D_1, D_2, D_3, and D_4 dopaminergic and α_2-adenergic receptors

(Pierce and Peroutka 1989; Peroutka 1994; Marona-Lewicka and Nichols 1995; Watts et al. 1995; Nichols et al. 2002). The fact that LSD acts at multiple serotonergic *and* catecholaminergic receptors may contribute to its biphasic locomotor profile. Studies have demonstrated that MAO_A inhibitors increase intracellular and extracellular concentrations of dopamine and noradrenaline (Buu 1989; Juorio et al. 1994; Iurlo et al. 2001). It is possible that the effects of MAO_A inhibitors on catecholaminergic systems are involved in the ability of these agents to shift the effects of 5-MeO-DMT to a LSD-like behavioral profile. Additional studies are required to determine whether the neurochemical effects of MAO_A inhibitors on dopaminergic and noradrenergic systems contribute to the behavioral interaction with 5-MeO-DMT.

The discriminative stimulus effects of LSD occur in two distinct temporal phases (Marona-Lewicka et al. 2005) that appear to parallel the biphasic locomotor effects of the drug. Marona-Lewicka and colleagues (Marona-Lewicka et al. 2005) have suggested that these behavioral phenomena in rats may correspond to the two temporal phases of LSD-induced subjective effects that have been noted in clinical studies (Freedman 1968, 1984). The present findings indicate that the behavioral effects of 5-MeO-DMT in the presence of MAO_A inhibitors also occur in two temporal phases. These results suggest that humans ingesting ayahuasca or ayahuasca-like preparations containing an indoleamine combined with a MAO inhibitor may experience drug effects in time-dependent phases. Regardless of the mechanism(s) by which the interaction of MAO_A inhibitors and 5-MeO-DMT occurs, it is clear from this study that these compounds have unique behavioral effects when administered in combination. Future studies will examine whether there are behavioral interactions between MAO_A inhibitors and DMT, and whether an interaction occurs when ayahuasca constituents are administered via the peroral route.

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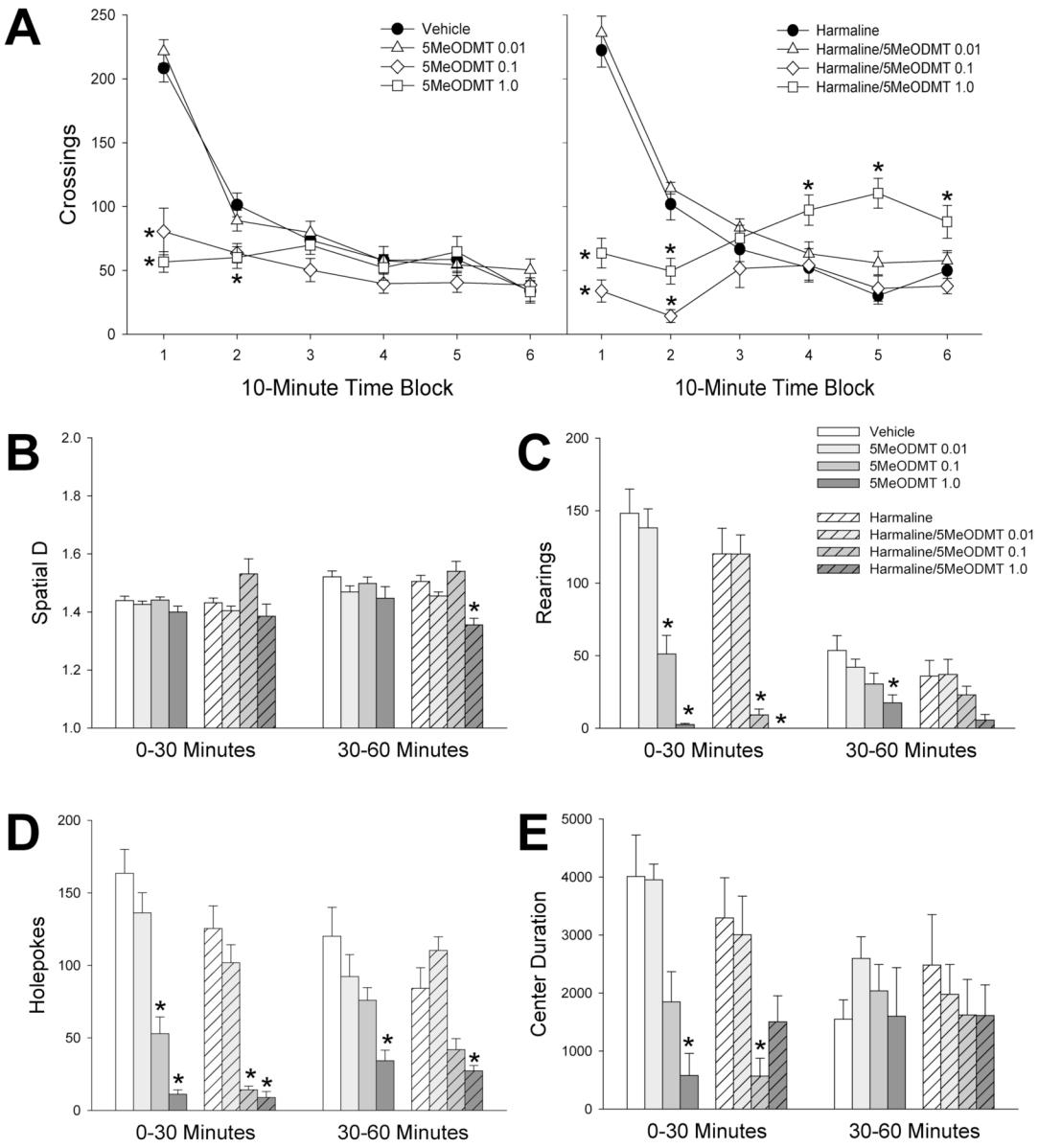

Figure 1.

Effect of harmaline pretreatment on the behavioral response to 5-MeO-DMT (a–e). Effect on (a) crossings, (b) spatial d, (c) number of rearings, (d) number of holepokes, and (e) time spent in the center (duration in tenths of sec). Data are expressed as group means±SEM for successive 10 min intervals (a), or group means±SEM (b–e). Drug doses are given in mg/kg. *$p<0.05$, significant difference from vehicle control group.

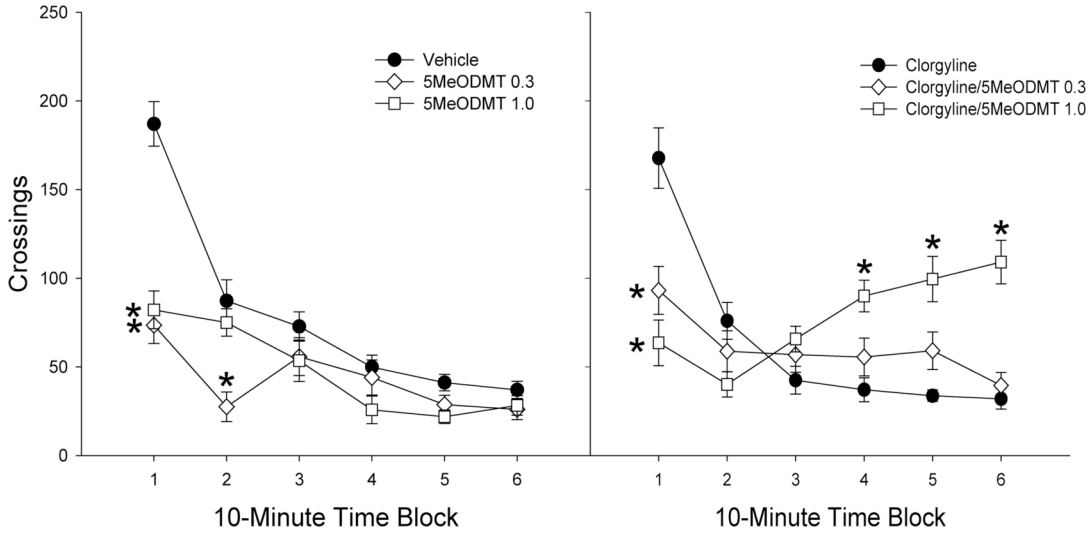

Figure 2.

Modification of the effect of 5-MeO-DMT on locomotor activity by clorgyline pretreatment. Crossings are expressed as group means±SEM for successive 10 min intervals of the 1-h test session. Drug doses are given in mg/kg. *p<0.05, significant difference from vehicle control group.

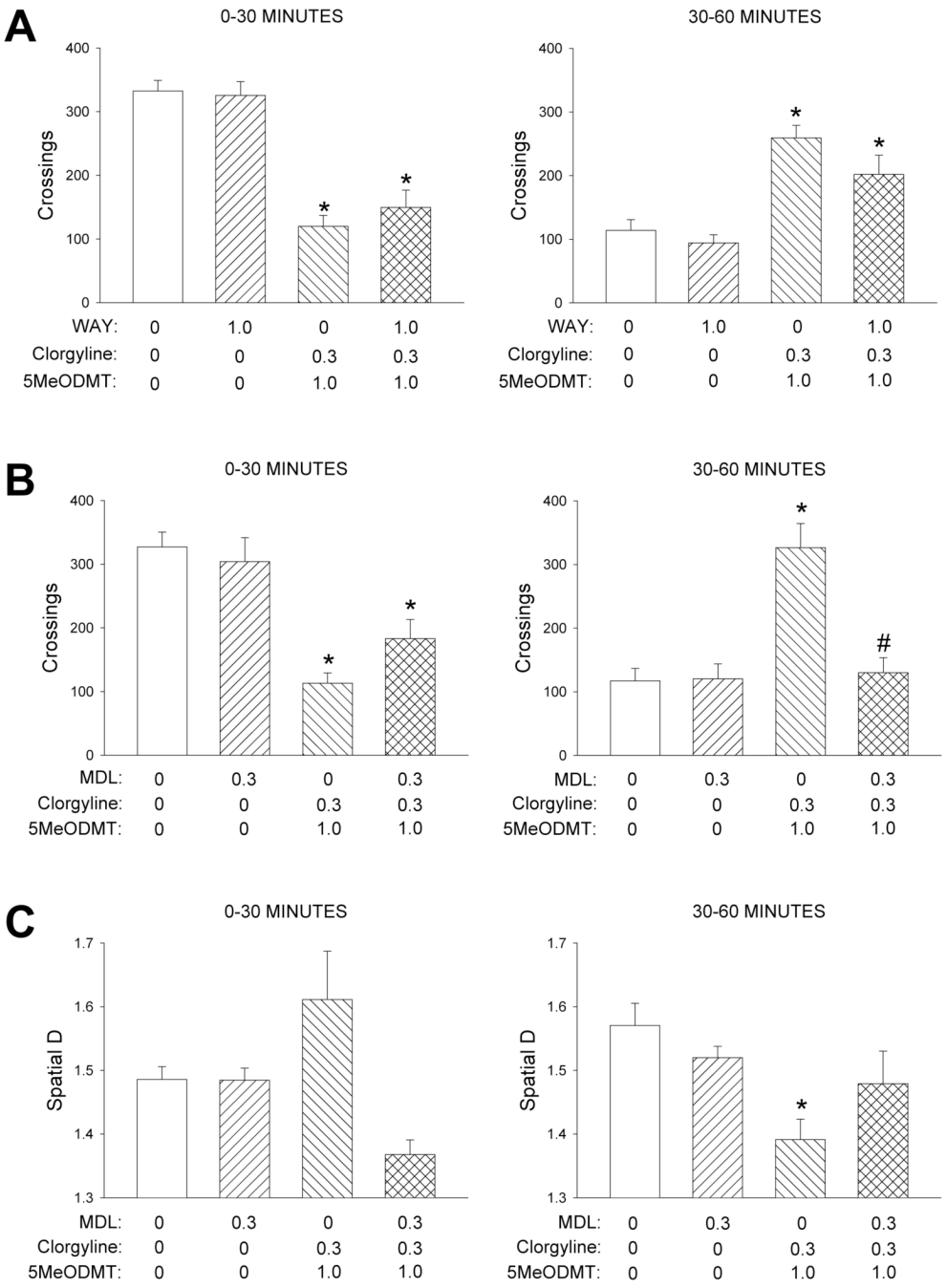

Figure 3.

Effect of WAY-100635 and MDL 11,939 on the behavioral response to clorgyline and 5-MeO-DMT. (a) Effect of WAY-100635 on crossings. (b) Effect of MDL 11,939 on crossings. (c) Effect of MDL 11,939 on spatial d. Data are presented as group means±SEM. Drug doses are given in mg/kg. *$p<0.05$, significant difference from vehicle control group. #$p<0.05$, significant difference from animals given only clorgyline and 5-MeO-DMT.

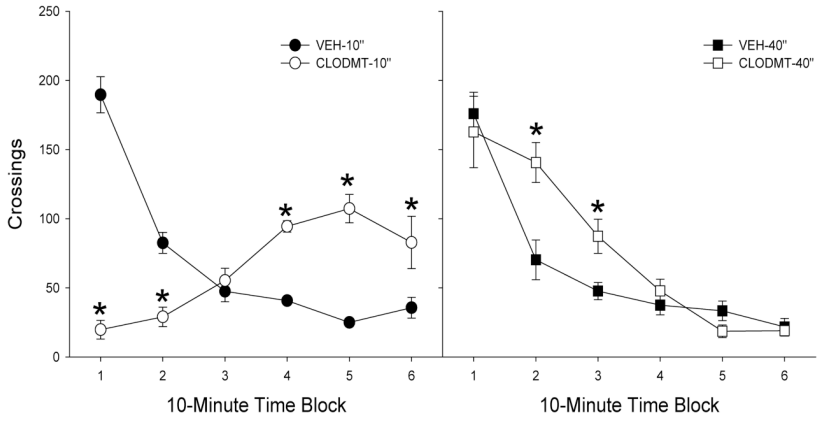

Figure 4.

Effect of varying the interval between drug treatment and testing on the behavioral response to clorgyline and 5-MeO-DMT. Animals were tested either 10 min after treatment (CLODMT-10″) or 40 min after treatment (CLODMT-40″). Crossings are shown as group means±SEM for successive 10 min intervals. *$p<0.05$, significant difference from vehicle control group.