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Behavioral effects of α,α,β,β-tetradeutero-5-MeO-DMT in rats: comparison with 5-MeO-DMT administered in combination with a monoamine oxidase inhibitor

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Abstract

RATIONALE—Ayahuasca is a psychoactive tea prepared from a combination of plants that contain a hallucinogenic tryptamine and monoamine oxidase inhibitors (MAOIs). Behavioral Pattern Monitor (BPM) experiments demonstrated that the combination of 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) and a behaviorally inactive dose of an MAO_A inhibitor such as harmaline or clorgyline induces biphasic effects on locomotor activity in rats, initially reducing locomotion and then increasing activity as time progresses.

OBJECTIVES—The present study investigated whether the biphasic locomotor profile induced by the combination of 5-MeO-DMT and an MAOI is a consequence of a reduction in the rate of 5-MeO-DMT metabolism. This hypothesis was tested using a deuterated derivative of 5-MeO-DMT (α,α,β,β-tetradeutero-5-MeO-DMT) that is resistant to metabolism by MAO.

RESULTS—Confirming our previous findings, 1.0 mg/kg 5-MeO-DMT (s.c.) had biphasic effects on locomotor activity in rats pretreated with a behaviorally inactive dose of the nonselective MAOI pargyline (10 mg/kg). Administration of 5-MeO-DMT alone, even at doses greater than 1.0 mg/kg, produced only reductions in locomotor activity. Although low doses of α,α,β,β-tetradeutero-5-MeO-DMT (0.3 and 1.0 mg/kg, s.c.) produced only hypoactivity in the BPM, a dose of 3.0 mg/kg induced a biphasic locomotor profile similar to that produced by the combination of 5-MeO-DMT and an MAOI. Receptor binding studies demonstrated that deuterium substitution had little effect on the affinity of 5-MeO-DMT for a wide variety of neurotransmitter binding sites.

CONCLUSIONS—The finding with α,α,β,β-tetradeutero-5-MeO-DMT indicates that the hyperactivity induced by 5-MeO-DMT after MAO inhibition is a consequence of reduced metabolism of 5-MeO-DMT, leading to prolonged occupation of central serotonin receptors. These results demonstrate that deuterated tryptamines may be useful in behavioral and pharmacological studies to mimic the effects of tryptamine/MAOI combinations.

Keywords

Ayahuasca; hallucinogen; kinetic isotope effect; locomotor activity; 5-methoxy-*N,N*-dimethyltryptamine; monoamine oxidase; deutero-5-MeO-DMT

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The serotonergic hallucinogens are a class of agents capable of producing a complex syndrome of mental and perceptual alterations, including profound distortions of perceptual processes, increased intensity and lability of affective responses, and changes in thought and cognition (Nichols 2004). Structurally, classical hallucinogens can be divided into two classes of compounds: (1) indoleamines such as *N,N*-dimethyltryptamine (DMT) and lysergic acid diethylamide (LSD), which bind non-selectively to serotonin (5-HT) receptors, and (2) phenylalkylamines such as mescaline and 2,5-dimethoxy-4-bromoamphetamine (DOB), which bind selectively to 5-HT_{2A} and 5-HT_{2C} receptors. There is extensive evidence, from both human and animal studies, that the characteristic effects of the indoleamine and phenylalkylamine hallucinogens are mediated by activation of the 5-HT_{2A} receptor (for reviews, see: Nichols 2004; Halberstadt and Geyer 2011). For example, most of the effects of psilocybin in human volunteers are blocked by the 5-HT_{2A} antagonist ketanserin (Vollenweider et al. 1998; Carter et al. 2005, 2007).

A variety of animal behavioral paradigms, including drug discrimination, prepulse inhibition of startle, and head twitch response, have been used to study hallucinogen effects in rodents (reviewed by: Halberstadt and Geyer 2011). We have also used the Behavioral Pattern Monitor (BPM) to test the effects of hallucinogens (Halberstadt and Geyer 2011). The BPM is a combination of activity and holeboard chambers that assesses both the quantity and quality of unconditioned locomotor and investigatory responding, and can characterize drug effects on spatiotemporal patterns of activity and responsiveness to environmental stimuli (Geyer et al. 1986; Geyer 1990). When phenylalkylamine and indoleamine hallucinogens are tested in rats in a novel BPM environment, they produce a characteristic behavioral profile that includes reductions of locomotor activity and investigatory behavior, and increased avoidance of the center of the BPM chamber (Geyer et al. 1979; Adams and Geyer 1985a; Wing et al. 1990; Halberstadt and Geyer 2011). LSD has similar effects on investigatory behavior and center avoidance (Adams and Geyer 1985b), but it produces a biphasic locomotor profile where activity is initially reduced and then increases over time (Mittman and Geyer 1991). Importantly, most of the effects of phenylalkylamine hallucinogens in the BPM are blocked by pretreatment with 5-HT_{2A} antagonists (Wing et al. 1990; Krebs-Thomson et al. 1998).

Ayahuasca is a hallucinogenic beverage used as a sacrament by indigenous populations throughout the Amazon basin of South America, as well as by syncretic religious groups in Brazil and New Mexico. Ayahuasca is prepared from the jungle liana *Banisteriopsis caapi*, which contains β-carboline alkaloids such as harmaline and harmine, in combination with DMT-containing plants such as *Psychotria viridis* or *Diplopterys cabrerana* (Schultes and Hofmann 1980; McKenna et al. 1984; Schultes and Raffauf 1990). DMT by itself is not orally active due to extensive first-pass metabolism, but harmaline and harmine are MAO_A inhibitors that block DMT catabolism (Agurell et al. 1968). Hence, by mixing extracts of one plant containing DMT with another plant containing β-carbolines, DMT becomes active orally in the form of an infusion or decoction.

We have used the BPM to test whether there are behavioral interactions between Ayahuasca constituents. Because of the very short-acting nature of DMT in rats, it is a difficult drug to use in extended behavioral studies. The hallucinogen 5-methoxy-DMT (5-MeO-DMT), which is also found in some Ayahuasca preparations and in many other plant extracts used in ritual settings (Holmstedt et al. 1980; Schultes and Raffauf 1995), has pharmacology similar to DMT (Glennon et al. 1982) and is easier to use in animal studies because it is longer-acting (Krebs-Thomson et al. 2006). Hence, our previous studies used a combination of 5-MeO-DMT and an MAO inhibitor as an approximation of Ayahuasca (Halberstadt et al. 2008). 5-MeO-DMT produces a short-lived decrease in exploratory behavior in rats in the BPM (Krebs-Thomson et al. 2006). However, after pretreatment with a behaviorally inactive

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dose of an MAO_A inhibitor, 5-MeO-DMT induces biphasic effects on locomotor activity, with activity initially reduced and then elevated as time progresses (Halberstadt et al. 2008). The hyperactivity is accompanied by a reduction of the measure spatial d, indicating an increase in the smoothness of the locomotor pattern. As was noted above, this behavioral profile was previously observed only with the hallucinogen LSD (Mittman and Geyer 1991; Krebs-Thomson et al. 1998; Grailhe et al. 1999). As was found with LSD (Mittman and Geyer 1991; Ouagazzal et al. 2001), the delayed hyperactivity produced by 5-MeO-DMT in combination with an MAO_A inhibitor is blocked by a selective 5-HT_{2A} antagonist (MDL 11,939) (Halberstadt et al. 2008).

The primary route of 5-MeO-DMT metabolism is oxidative deamination by MAO_A (Agurell et al. 1969; Sitaram et al. 1987b), and there is evidence that MAO inhibitors alter 5-MeO-DMT pharmacokinetics (Squires 1975; Sitaram et al. 1987a). Thus, it is possible that the ability of 5-MeO-DMT to produce delayed hyperactivity in the presence of MAO inhibitors is a consequence of a reduction in the rate of 5-MeO-DMT deamination by MAO_A. It is well established that α-deutero substitution in the ethylamine side-chain of tryptamines induces resistance to metabolism by MAO via the kinetic isotope effect (Beaton et al. 1982; Barker et al. 1982, 1984; Dyck and Boulton 1986). Indeed, after α,α,β,β-tetradeuteration of DMT, higher brain levels are achieved and clearance time is increased (Barker et al. 1982). Hence, we tested whether a deuterated derivative of 5-MeO-DMT (α,α,β,β-tetradeutero-5-MeO-DMT; Shaw et al. 1977) can reproduce the behavioral profile produced by 5-MeO-DMT and an MAO inhibitor. Receptor binding studies were also conducted to compare the affinities of 5-MeO-DMT and α,α,β,β-tetradeutero-5-MeO-DMT for a variety of neurotransmitter receptors and transporters. The structures of 5-MeO-DMT and α,α,β,β-tetradeutereo-5-MeO-DMT are shown in Figure 1.

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 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

Locomotor activity and patterns were measured in the Behavioral Pattern Monitor (BPM), a 30.5 × 61.0 × 28.0 cm black Plexiglas chamber. The animal's position in an X–Y plane was detected by a 4 × 8 grid of infrared photobeams. A computer continuously monitored the status of the photobeams and stored the data for subsequent off-line analysis. For a more detailed description of the BPM, see: (Geyer et al. 1986). The BPM also records investigatory behaviors such as rearing and holepokes, but those data are not reported herein because there is no specific interaction between 5-MeO-DMT and MAO inhibitors for those behavioral measures (see: Halberstadt et al. 2008).

Procedure

One day prior to testing in the BPM, rats were taken to the testing room, weighed, handled briefly, placed in a clear Plexiglas box (24 × 46 cm) for approximately 30 s, and then

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returned to their home cages in the animal colony. On the testing day, animals were brought to the testing room and allowed to sit for 60 min before receiving injections. Injections were administered in the testing room under red lights. Animals were tested during the dark phase in darkness. Animals were placed in the BPM chambers 10 min after treatment with 5-MeO-DMT or α,α,β,β-tetradeutero-5-MeO-DMT, and behavior monitored for 60 min. In experiment 1, rats (n=7–8, 61 total) were treated with the nonselective MAO inhibitor pargyline (0 or 10 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, 31 total) were treated with α,α,β,β-tetradeutero-5-MeO-DMT (0, 0.3, 1.0, or 3.0 mg/kg. In experiment 3, rats (n=6–7, 27 total) were treated with 5-MeO-DMT (0, 0.3, 1.0, or 3.0 mg/kg). The animals tested for these experiments were all naïve to the BPM chambers.

Analysis

The raw data were reduced to the X and Y coordinates of the rat in the chamber. Further analyses produced specific measures of behavior (Geyer et al. 1986). Locomotor activity was quantified by the number of crossings between eight equal square sectors within the BPM. Analysis of the spatial structure of locomotor paths was performed by calculating a descriptive statistic, spatial d. The statistic spatial d is based conceptually on fractal geometry and calculated using scaling arguments (for a detailed description, see: Paulus and Geyer 1991). Changes in spatial d reflect smoother (decreases in spatial d) or rougher (increases in spatial d) locomotor paths. Locomotor data were examined in 10-min time blocks, and spatial d data were examined in 30-min time blocks. Data were analyzed using two- or three-way analysis of variance with pretreatment and treatment as between-subject 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 α level of 0.05.

Drugs

5-Methoxy-*N, N*-dimethyltryptamine oxalate (5-MeO-DMT) and pargyline hydrochloride were obtained from Sigma-Aldrich (St. Louis, MO, USA). α,α,β,β-Tetradeutero-5-methoxy-*N,N*-dimethyltryptamine (2:1) fumarate (α,α,β,β-tetradeutero-5-MeO-DMT) was prepared in the laboratory of Dr. David Nichols by reduction of 2-(5-methoxy-3-indolyl)-*N,N*-dimethylglyoxylamide with lithium aluminum deuteride. The synthetic material met analytical criteria for ^{1}H NMR, mass spectrum, and elemental analysis. Doses of pargyline are expressed as the salt form of the drug, and doses of 5-MeO-DMT and α,α,β,β-tetradeutero-5-MeO-DMT refer to the freebase. 5-MeO-DMT, α,α,β,β-tetradeutero-5-MeO-DMT, and pargyline were dissolved in isotonic saline. All drugs were administered subcutaneously in a volume of 1 ml/kg.

RESULTS

Experiment 1

As shown in Fig. 2a, treatment with 0.1 and 1.0 mg/kg 5-MeO-DMT reduced crossings in vehicle-pretreated animals, leading to a main effect of treatment [F(3,53)=13.54, p<0.0001], and an interaction between treatment and time [F(15,265)=42.92, p<0.0001]. Consistent with our previous findings (Halberstadt et al., 2008), there was an interaction of pargyline pretreatment and 5-MeO-DMT treatment [F(3,53)=5.36, p=0.0027], and a three-way interaction between pretreatment, treatment, and time [F(15,265)=3.62, p<0.0001]. Indeed, in animals pretreated with pargyline, 1.0 mg/kg 5-MeO-DMT altered crossings in a biphasic manner, *reducing* locomotor activity during the first half-hour of the session and then *increasing* activity during the second half-hour (p<0.01, Tukey's test; Fig. 2a). By contrast, the combination of pargyline and 0.1 mg/kg 5-MeO-DMT reduced crossings during the first

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half-hour, but did not increase activity during the second half-hour. There was an interaction of pargyline pretreatment and time [$F(5,265)=18.32$, $p<0.0001$], but post hoc analysis failed to confirm this effect for any 10-min time block.

Pargyline [pretreatment × time: $F(1,55)=18.14$, $p=0.0001$] and 5-MeO-DMT [treatment × time: $F(3,53)=5.62$, $p=0.002$] altered spatial d, a measure of the complexity of locomotor paths, but post hoc analysis failed to confirm this for any specific 30-min block. More importantly, there was a significant three-way interaction between pargyline pretreatment, 5-MeO-DMT treatment, and time [$F(3,53)=12.36$, $p<0.0001$]. As illustrated in Fig. 2b, 1.0 mg/kg 5-MeO-DMT significantly reduced spatial d during the second half-hour of the session in animals pretreated with pargyline ($p<0.01$, Tukey's test). The 0.01 and 0.1 mg/kg doses of 5-MeO-DMT had no effect on spatial d in pargyline-pretreated animals.

Experiment 2

α,α,β,β-Tetradeutero-5-MeO-DMT treatment had a significant main effect on crossings [$F(3,27)=14.68$, $p<0.0001$], and interacted with time [$F(15,135)=23.93$, $p<0.0001$]. Post-hoc analysis demonstrated that the 0.3, 1.0, and 3.0 mg/kg doses of tetradeutero-5-MeO-DMT significantly *reduced* crossings during the first 20 min of the session (Fig. 3a). Confirming the primary hypothesis, the 3.0 mg/kg dose of tetradeutero-5-MeO-DMT significantly *increased* crossings during the fifth 10-min time block ($p<0.01$, Tukey's test). Rats treated with 3.0 mg/kg of deuterated-5-MeO-DMT displayed more than twice the amount of locomotor activity exhibited by animals treated with vehicle (107.5±8.5 crossings (mean ±S.E.M.) versus 51.8±7.3 crossings, respectively) during that time block. Neither of the lower doses tested (0.3 and 1.0 mg/kg) induced a delayed increase in activity.

For spatial d, there was a significant main effect of treatment with α,α,β,β-tetradeutero-5-MeO-DMT [$F(3,27)=5.14$, $p<0.007$], and a significant interaction between treatment and time [$F(3,27)=21.92$, $p<0.0001$]. As shown in Figure 3b, specific comparisons revealed that compared to vehicle treatment 3.0 mg/kg α,α,β,β-tetradeutero-5-MeO-DMT significantly increased spatial d during the first 30 min of the session ($p<0.01$, Tukey's test) and significantly reduced spatial d during the second 30 min of the session ($p<0.01$).

Experiment 3

We previously reported (Krebs-Thompson et al. 2006) that administration of 5-MeO-DMT at doses of 0.01-1.0 mg/kg produces a short-lived reduction in locomotor activity in the BPM. To examine the behavioral response to higher doses of 5-MeO-DMT, we tested the drug at doses ranging from 0.3 to 3.0 mg/kg. As expected, there was a significant main effect of treatment [$F(3,23)=5.73$, $p<0.005$] and a significant interaction between treatment and time [$F(15,115)=8.39$, $p<0.0001$]. As we found previously, 5-MeO-DMT significantly reduced crossings during the first 10 min of testing ($p<0.01$, Tukey's test; Fig. 4a). Importantly, 5-MeO-DMT did not induce biphasic effects on locomotor activity, even when tested at 3 mg/kg.

There was an increase in spatial d after administration of 5-MeO-DMT, yielding an interaction between treatment and time that approached but did not reach significance [$F(3,23)=2.41$, $p<0.1$]. However, post hoc analysis revealed that 5-MeO-DMT failed to alter spatial d significantly during either the first or the second half-hour of testing (Fig. 4b).

Radioligand binding experiments

Receptor binding studies were performed by the NIMH Psychoactive Drug Screening Program (NIMH PDSP). The binding affinities of 5-MeO-DMT and α,α,β,β-tetradeutero-5-MeO-DMT for a variety of receptor sites are listed in Table 1. 5-MeO-DMT displays

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moderate to high affinity for most 5-HT receptors, and has moderate affinity for α- and β-adrenergic receptor subtypes, the 5-HT transporter (SERT), and sigma-2 binding sites. 5-MeO-DMT binds with lower affinity to dopamine receptors, histamine receptors, opiate receptors, dopamine (DAT) and norepinephrine (NET) transporters, and sigma-1 binding sites. The effect of tetradeuteration on the binding profile of 5-MeO-DMT is generally unremarkable except for serotonergic 5-HT_{1B} and adrenergic α_{1A} receptors where the deuterium-substituted compound binds with approximately 4-fold higher affinity than proteo-5-MeO-DMT.

DISCUSSION

We previously reported that administration of 1 mg/kg 5-MeO-DMT in combination with an MAO_A inhibitor such as clorgyline or harmaline induced a biphasic locomotor profile where activity was initially reduced and then increased as time progressed (Halberstadt et al. 2008). The delayed hyperactivity was accompanied by a decrease in spatial d, suggesting the animals made smoother locomotor paths. The present studies have confirmed those earlier findings by showing that the combination of 5-MeO-DMT and the nonselective MAO inhibitor pargyline also induces a biphasic locomotor profile and a reduction in spatial d. The experiments demonstrated that the interaction between 5-MeO-DMT and MAO inhibitors is extremely dose dependent, occurring with 1 mg/kg 5-MeO-DMT but not with 0.3 mg/kg. Furthermore, we found that 5-MeO-DMT alone does not induce delayed hyperactivity, even if administered at doses > 1 mg/kg.

The dose of pargyline used in the present investigation (10 mg/kg, s.c.) non-selectively inhibits MAO (78% MAO_A inhibition vs. 92% MAO_B inhibition; Ortmann et al. 1984). We previously demonstrated that treatment with either the MAO_A inhibitor harmaline or a low dose of the selective MAO_A inhibitor clorgyline transforms the effect of 5-MeO-DMT to a biphasic locomotor profile, whereas the selective MAO_B inhibitor (–)-deprenyl is ineffective (Halberstadt et al. 2008). Given those earlier findings, it is likely that MAO_A inhibition by pargyline is responsible for the interaction with 5-MeO-DMT. Although there is some evidence that pargyline can bind to sites other than MAO_A and MAO_B, it is unlikely that those effects contribute to the interaction with 5-MeO-DMT. Clorgyline, harmaline, and pargyline have been shown to bind to imidazoline I_2 receptors (Lione et al. 1996; Husbands et al. 2001; Miralles et al. 2005). However, binding to I_2 receptors probably does not play a role in the interaction because (–)-deprenyl binds to I_2 receptors with roughly the same affinity as clorgyline (Lione et al. 1996) yet fails to interact with 5-MeO-DMT. Likewise, it has been reported that pargyline and clorgyline bind to σ receptors (Itzhak and Kassim, 1990) and to an MAOI-displaceable quinpirole binding site (MQB; Levant et al. 1996), but (–)-deprenyl also binds to these sites with moderately high affinity.

As discussed previously (Halberstadt et al. 2008), there are at least two potential explanations for the behavioral interactions between 5-MeO-DMT and MAO_A inhibitors. First, 5-MeO-DMT pharmacokinetics are altered by pretreatment with a MAO inhibitor (Squires 1975; Sitaram et al. 1987a; Shen et al. 2010a,b), so it is possible that the ability of 5-MeO-DMT to induce delayed hyperactivity when administered in combination with a MAO inhibitor is due to a reduction in the rate of 5-MeO-DMT metabolism by MAO_A. Second, MAO inhibition could alter 5-MeO-DMT pharmacodynamics, including the downstream neurochemical response to the drug. For example, 5-MeO-DMT can enhance the firing of dopaminergic neurons (Christoph et al. 1977; White and Wang 1983), and this effect could be altered by MAOI-induced changes in dopamine metabolism. We hypothesized that if the ability of MAO inhibitors to alter the behavioral effects of 5-MeO-DMT is due to a pharmacokinetic interaction, then α,α,β,β-tetradeutero-5-MeO-DMT should produce a similar behavioral profile because it is more resistant to metabolism by MAO as a

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result of a kinetic isotope effect. Importantly, we found that α,α,β,β-tetradeutero-5-MeO-DMT alone produces a biphasic locomotor profile and a delayed reduction of spatial d. Because α,α,β,β-tetradeutero-5-MeO-DMT does not inhibit MAO, this finding completely eliminates the possibility that neurochemical changes subsequent to MAO inhibition are responsible for the delayed hyperactivity. Instead, this finding supports the hypothesis that the biphasic behavioral profile is a consequence of altered 5-MeO-DMT pharmacokinetics.

Like other indoleamine hallucinogens, 5-MeO-DMT is an agonist at 5-HT_{1A} and 5-HT_{2A} receptors (Halberstadt & Geyer 2011). Our previous experiments have shown that the hyperactivity induced by 5-MeO-DMT in combination with an MAO inhibitor is blocked by the highly selective 5-HT_{2A} antagonist MDL 11,939 but unaffected by the selective 5-HT_{1A} antagonist WAY-100,635 (Halberstadt et al. 2008). Based on those findings, we have concluded that the hyperactivity is mediated by 5-HT_{2A} receptor activation. The fact that the binding profiles of 5-MeO-DMT and α,α,β,β-tetradeutero-5-MeO-DMT at 5-HT receptors are very similar indicates that differences in receptor affinity are unlikely to be responsible for the behavioral differences between these two compounds.

As was noted earlier, there is strong support for a link between 5-HT_{2A} receptor activation and hallucinogenic effects (Nichols 2004; Halberstadt & Geyer 2011). Given that 5-MeO-DMT is a potent hallucinogenic agent that is active in humans at parenteral doses of 2-3 mg (Shulgin and Shulgin 1997), it is surprising that this compound displayed relatively low (~ 0.9 μM) affinity for the 5-HT_{2A} receptor. It is important to note, however, that 5-HT_{2A} receptors exist in high-affinity and low-affinity agonist binding conformations depending on whether they are coupled to G proteins. 5-HT_{2A} antagonists such as [^{3}H]ketanserin label both states with equal affinity, whereas radiolabeled agonists such as [^{3}H]DOB bind selectively to the G protein-coupled, high-affinity state of the receptor (Glennon et al. 1988; Lyon et al. 1987). The binding affinity of agonists for the 5-HT_{2A} receptor varies depending on whether the receptor is radiolabeled with an agonist or an antagonist, and agonists generally display 10-100-fold higher affinity for agonist-labeled 5-HT_{2A} receptors compared with antagonist-labeled receptors (Titeler et al. 1988; Glennon et al. 1992, 1994). Since the 5-HT_{2A} binding data listed in Table I were obtained using [^{3}H]ketanserin, they likely underestimate the affinity of 5-MeO-DMT and α,α,β,β-tetradeutereo-5-MeO-DMT for the high-affinity state of the receptor. Indeed, it was previously reported that 5-MeO-DMT binds to [^{3}H]DOB-labeled 5-HT_{2A} receptors with a K_i of 90 nM (Egan et al. 2000), which is 10-fold greater than the value reported herein.

We have previously demonstrated that the time course of the biphasic locomotor effects induced by the combination of MAO inhibitors and 5-MeO-DMT is dependent on the time delay between injection and testing (Halberstadt et al. 2008). This finding indicates that the biphasic effects reflect distinct temporal phases of drug action, as opposed to an interaction of the drug and the amount of time spent in the BPM chamber. The major route of 5-MeO-DMT metabolism is oxidative deamination by MAO_A (Agurell et al. 1969; Sitaram et al. 1987b), but 5-MeO-DMT is also *O*-demethylated to bufotenine (5-hydroxy-DMT) by cytochrome P450 2D6 (Agurell et al. 1969; Yu et al. 2003). Importantly, bufotenine is a highly efficacious 5-HT_{2A} agonist with 10-fold higher affinity for the 5-HT_{2A} receptor than 5-MeO-DMT (Roth et al. 1997; Egan et al. 2000). It was demonstrated recently that conversion of 5-MeO-DMT to bufotenine is markedly increased in mice pretreated with the MAO_A inhibitor harmaline (Shen et al. 2010a,b). In light of that finding, we hypothesize that the delayed hyperactive phase induced by 5-MeO-DMT in the presence of an MAO_A inhibitor is a consequence of conversion of 5-MeO-DMT to bufotenine, which produces hyperactivity via 5-HT_{2A} receptor activation. Although 5-HT_{2A} agonists typically reduce activity in rats (Wing et al. 1990; Krebs-Thomson et al. 1998; Hameleers et al. 2007), there is some evidence that high doses of 5-HT_{2A} agonists can increase locomotor activity

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(Yamamoto and Ueki 1975; Pálenícek et al. 2008). Bufotenine is deaminated by MAO (Gessner et al. 1960), and high levels could potentially accumulate in the brain after MAO inhibition. Studies are in progress to determine whether the time course of hyperactivity produced by 5-MeO-DMT and an MAO inhibitor is temporally correlated with bufotenine brain levels. Many tryptamine derivatives are metabolized by 6-hydroxylation (Szara and Axelrod 1959; Kopin et al. 1961; Szara 1961; Szara et al. 1962), and thus it is also possible that 6-hydroxy-5-methoxy-DMT may contribute to the hyperactivity produced by 5-MeO-DMT and an MAO_A inhibitor. However, 6-hydroxy-5-methoxy-DMT has yet to be conclusively identified as a metabolite of 5-MeO-DMT in rats (Agurell et al. 1969). Although the route for metabolism of α,α,β,β-tetradeutero-5-MeO-DMT has not been characterized, it is anticipated that the biotransformation of that compound would be very similar to that of 5-MeO-DMT in the presence of an MAO inhibitor. Thus, it is possible that the hyperactivity induced by α,α,β,β-tetradeutero-5-MeO-DMT could be a consequence of *O*-demethylation to α,α,β,β-tetradeutero-bufotenine. Future studies will compare the metabolism of 5-MeO-DMT and α,α,β,β-tetradeutero-5-MeO-DMT.

In summary, we have shown that the behavioral interaction between 5-MeO-DMT and MAO inhibitors is likely a consequence of altered 5-MeO-DMT pharmacokinetics. Indeed, a similar behavioral profile is produced by a deuterated derivative of 5-MeO-DMT that is resistant to metabolism by MAO. The results obtained with α,α,β,β-tetradeutero-5-MeO-DMT indicate that deuterated tryptamine derivatives may be useful as single-drug approximations of Ayahuasca. Furthermore, because deuteration has little apparent effect on receptor binding, these compounds may have utility in studies where it is desirable to use tryptamine derivatives that are not metabolically labile and thus have long-lasting pharmacological and behavioral effects. Given the complex pharmacokinetic and behavioral interactions that occur between tryptamine derivatives and MAO inhibitors, the present results indicate that interactions between Ayahuasca constituents need to be studied systematically in order to understand fully the mechanism of action of the botanical preparation. It is also important to note that 5-MeO-DMT has recently become popular as a "designer drug", often obtained from online vendors, and is now controlled in the United States as a Schedule I hallucinogen by the Drug Enforcement Administration (Anonymous 2010). There have been anecdotal reports that 5-MeO-DMT is sometimes ingested in combination with MAO inhibitors (Shulgin and Shulgin 1997; Ott 2001; Brush et al. 2004). Our findings indicate that these drug combinations may have distinct behavioral and toxicological effects compared with 5-MeO-DMT taken alone. Indeed, it has been reported that ingestion of a high dose of 5-MeO-DMT in combination with an MAO inhibitor resulted in a fatality (Sklerov et al. 2005). Studies are currently in progress to examine whether behavioral and pharmacokinetic interactions occur between MAO inhibitors and a variety of tryptamine derivatives.

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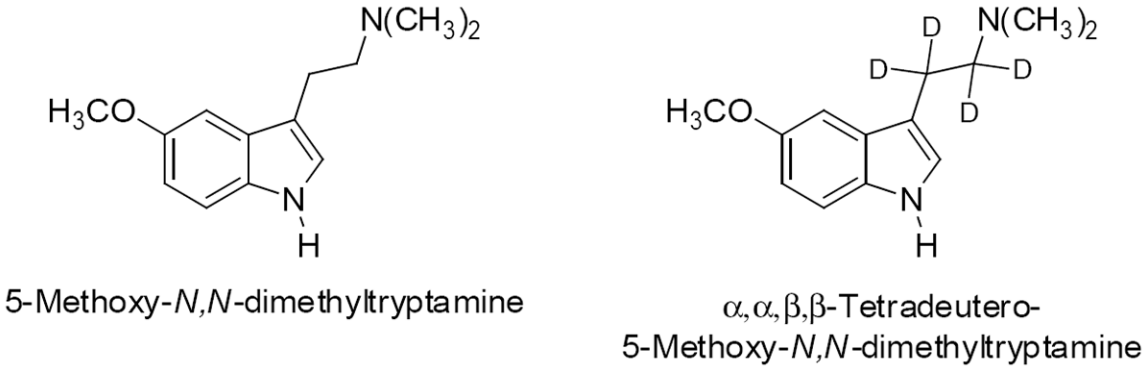

Figure 1.
Chemical structures of 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT, left) and α,α,β,β-tetradeutereo-5-MeO-DMT (right).

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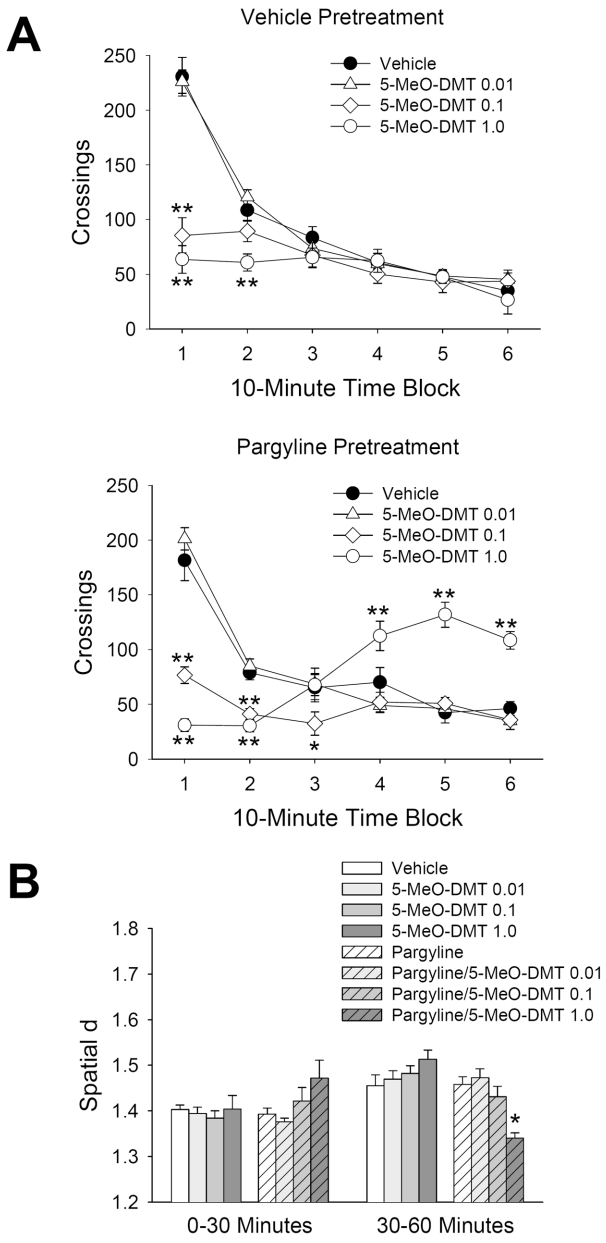

Figure 2.

Modification of the behavioral response to 5-MeO-DMT by pargyline pretreatment. (a) Effect of vehicle (●), 0.01 mg/kg (△), 0.1 mg/kg (◇), or 1.0 mg/kg (○) 5- MeO-DMT on crossings in animals pretreated with vehicle (top panel) or 10 mg/kg pargyline (bottom panel). (b) Effect on spatial d. Data are expressed as group means±SEM for successive 10 min intervals (a), or group means±SEM (b). Drug doses are given in mg/kg. *p<0.05, **p<0.01, significant difference from vehicle-vehicle control group.

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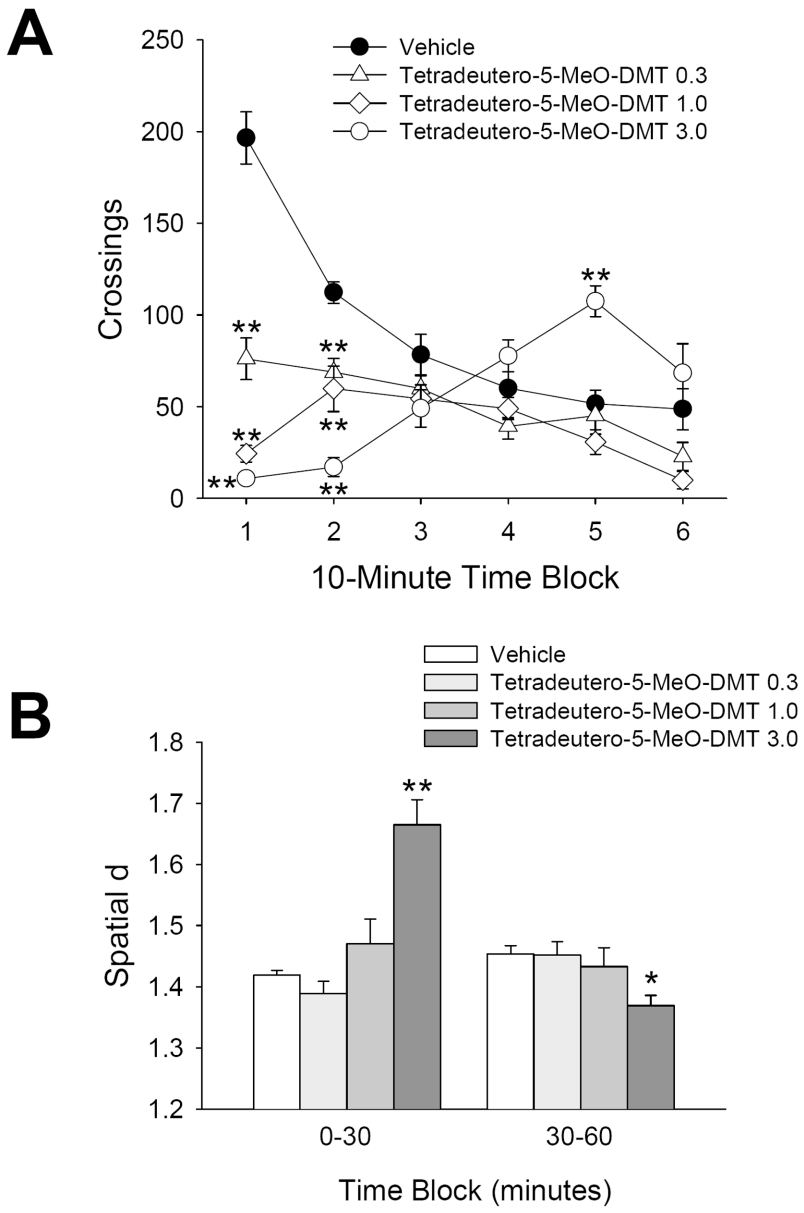

Figure 3.

Behavioral response to α,α,β,β-tetradeutero-5-MeO-DMT. (a) Effect of vehicle (●), 0.3 mg/kg (△), 1.0 mg/kg (◇), or 3.0 mg/kg (○) α,α,β,β-tetradeutero-5-MeO-DMT on crossings. (b) Effect on spatial d. Data are expressed as group means±SEM for successive 10 min intervals (a), or group means±SEM (b). Drug doses are given in mg/kg. *p<0.05, **p<0.01, significant difference from vehicle control group.

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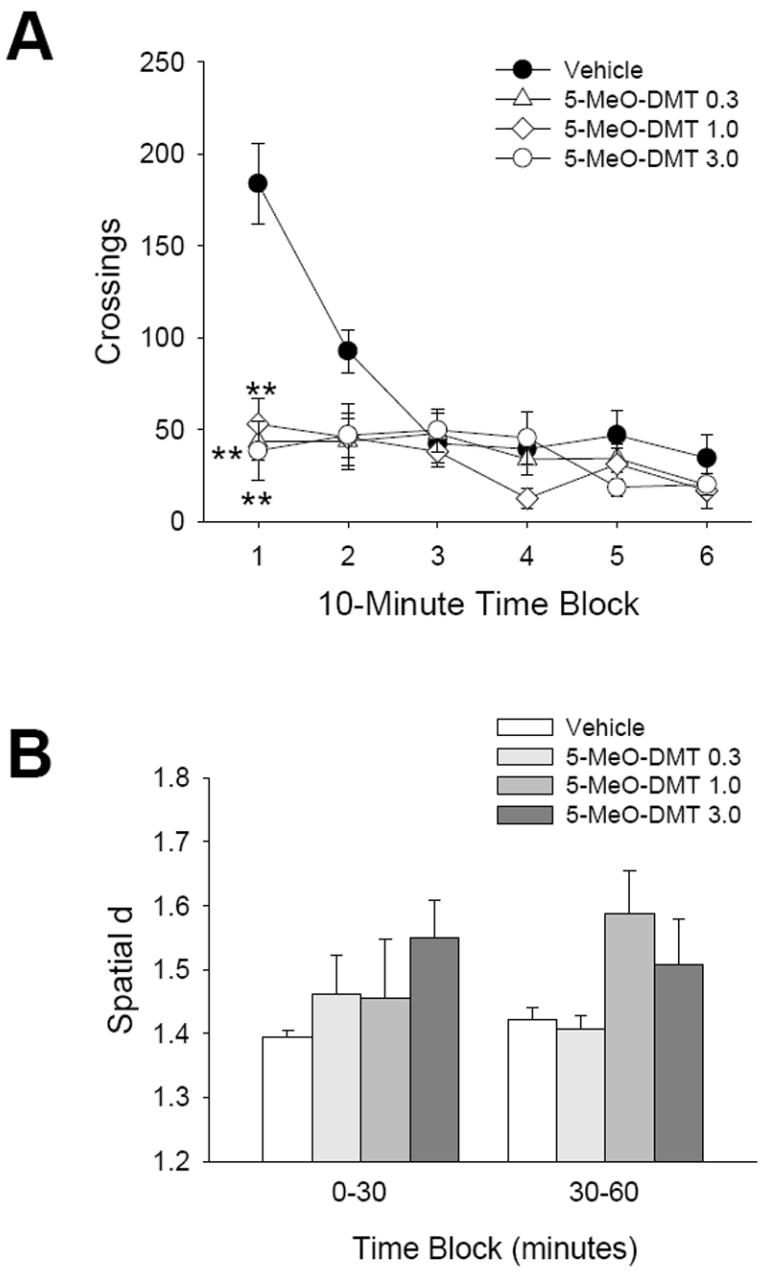

Figure 4.

Behavioral response to 5-MeO-DMT. (a) Effect of vehicle (●), 0.3 mg/kg (△), 1.0 mg/kg (◇), or 3.0 mg/kg (○) 5-MeO-DMT on crossings. (b) Effect on spatial d. Data are expressed as group means±SEM for successive 10 min intervals (a), or group means±SEM (b). Drug doses are given in mg/kg. **p<0.01, significant difference from vehicle control group.

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Table 1

Receptor binding data for 5-MeO-DMT and α,α,β,β-tetradeutero-5-MeO-DMT

Receptor	Radioligand	Species[a]	5-MeO-DMT K_i nM (±SEM)[b]	α,α,β,β-Tetradeutero-5-MeO-DMT K_i nM (±SEM)[b]
5-HT_{1A}	[^{3}H]8-OH-DPAT	Human	3.0 (0.2)	3.0 (0.4)
5-HT_{1B}	[^{3}H]GR125743	Human	14.0 (2)	3.5 (0.6)
5-HT_{1D}	[^{3}H]GR125743	Human	2.3 (0.3)	1.7 (0.3)
5-HT_{1E}	[^{3}H]5-HT	Human	376 (67)	483 (90)
5-HT_{2A}	[^{3}H]ketanserin	Human	907 (170)	1292 (243)
5-HT_{2B}	[^{3}H]LSD	Human	36 (6)	90 (14)
5-HT_{2C}	[^{3}H]mesulergine	Rat	418 (35)	286 (25)
5-HT_{5A}	[^{3}H]LSD	Human	505 (72)	151 (20)
5-HT_6	[^{3}H]LSD	Human	6.5 (1.2)	10.0 (1)
5-HT_7	[^{3}H]LSD	Human	4.5 (0.5)	2.6 (0.4)
α_{1A}	[^{3}H]prazocin	Human	4373 (354)	1013 (92)
α_{1B}	[^{3}H]prazocin	Human	2188 (219)	841 (67)
α_{1D}	[^{125}I]HEAT	Human	439 (52)	202 (17)
α_{2A}	[^{3}H]clonidine	Human	938 (56)	1871 (187)
α_{2B}	[^{3}H]clonidine	Human	430 (40)	513 (48)
α_{2C}	[^{3}H]clonidine	Human	206 (14)	274 (16)
β_2	[^{3}H]CGP12177	Human	2679 (238)	4560 (365)
D_3	[^{3}H]N-methyl-spiperone	Rat	> 10000	7087 (1125)
H_1	[^{3}H]pyrilamine	Human	7580 (1024)	> 10000
H_2	[^{3}H]tiotidine	Human	> 10000	7165 (853)
SERT	[^{3}H]citalopram	Human	3603 (559)	2761 (330)
Sigma-2	[^{3}H]DTG	Rat	3689 (336)	7171 (1156)

[a] The experiments were performed using cloned receptors.

[b] 5-MeO-DMT and α,α,β,β-tetradeutero-5-MeO-DMT bound to the following sites with K_i values > 10,000 nM: 5-HT_3, rat brain benzodiazepine site, Ca^{2+} channels, D_1, D_2, D_4, D_5, DAT, NET, β_1, β_3, DOR, MOR, KOR, EP_3, EP_4, $GABA_A$, H_3, H_4, M_1, M_2, M_3, M4, M_5, and sigma-1.