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Discriminative Stimulus Effects of N,N-Diisopropyltryptamine

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Abstract

Rationale—Serotonergic hallucinogens such as (+)-lysergic acid diethylamide (LSD) and dimethyltryptamine (DMT) produce distinctive visual effects, whereas the synthetic hallucinogen N,N-diisopropyltryptamine (DiPT) is known for its production of auditory distortions. **Objective:** This study compares the discriminative stimulus effects of DiPT to those of visual hallucinogens.

Methods—Adult male rats were trained to discriminate DiPT (5 mg/kg, 15 min) from saline under a FR10 schedule. A dose-effect and time course of DiPT's discriminative stimulus effects were established. DMT, (–)-2,5-dimethoxy-4-methylamphetamine (DOM), LSD, (±)-methylenedioxymethamphetamine (MDMA) and (+)-methamphetamine were tested for cross-substitution in DiPT-trained animals.

Results—Rats learned to discriminate DiPT from saline in an average of 60 training sessions (30 drug and 30 saline). DiPT (0.5 – 5 mg/kg) produced dose-dependent increases in drug-appropriate responding (DAR) to 99% (ED₅₀ = 2.47 mg/kg). Onset of the discriminative stimulus effects was within 5 minutes and the effects dissipated within 4 hours. Full substitution for the discriminative stimulus effects of DiPT occurred with LSD, DOM and MDMA. DMT only partially substituted for DiPT (65% DAR), whereas (+)-methamphetamine failed to substitute for DiPT (29% DAR).

Conclusions—The discriminative stimulus effects of DiPT were similar those of a number of synthetic hallucinogens, only partially similar to those of DMT, but not similar to (+)-methamphetamine. The putative DiPT-induced auditory distortions do not lead to discriminative stimulus effects distinguishable from other hallucinogens.

Keywords

N,N-Diisopropyltryptamine; hallucinogens; drug discrimination; rat

Introduction

Hallucinogens such as N,N-dimethyltryptamine (DMT) have been used for centuries. Spiritual rituals like those of the Amazonian cultures commonly included hallucinogens in the form of brews and teas such as *ayahuasca* and *yage* to gain spiritual insights. DMT is the active agent responsible for the brief episodic hallucinations that occur with *ayahuasca*. Although hallucinogens have a long history of use, relatively little research has been conducted in the laboratory.

N,N-diisopropyltryptamine (DiPT) is a synthetic hallucinogen structurally related to other tryptamine hallucinogens. Structurally, DiPT is most closely related to N,N-

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dimethyltryptamine (DMT), which produces short term visual hallucinations and bizarre dream states at high doses (Shulgin and Shulgin 1997; Strassman et al. 1996). However, unlike DMT and most serotonergic hallucinogens, DiPT may produce auditory effects. Anecdotal reports in human subject indicate that auditory distortion occurs with low doses, in which tones become deeper, and that auditory effects such as hearing voices occur with high doses (Shulgin and Carter, 1980; Shulgin and Shulgin 1997) and [erowid.org](https://www.erowid.org).

Studies assessing the molecular mechanisms of action have yet to be conducted to determine whether DiPT has a similar functional binding profile to other serotonin-mediated hallucinogens. What is known is that DiPT is an agonist at 5HT_{2A} receptors and a partial agonist at 5HT_{1A} receptors (Gatch et al. 2011), and that DiPT inhibits transport at serotonin transporter and vesicular monoamine transporter 2, but has little to no interaction with dopamine or norepinephrine transporters at concentrations less than 10 μ M (Cozzi et al. 2009; Gatch et al. 2011; Nagai et al. 2007).

Previously, the discriminative stimulus effects of DiPT were tested in different groups of rats trained to discriminate DMT, LSD, DOM, (+)-methamphetamine, cocaine and MDMA (Gatch et al. 2011). DiPT produced full substitution in rats trained to discriminate DMT and DOM, partial substitution in LSD-trained rats, and failed to substitute for MDMA, (+)-methamphetamine and cocaine. These findings, along with the molecular studies indicate that DiPT has similar actions as other hallucinogens. It should be noted that hallucinogenic compounds do not share completely overlapping discriminative stimulus effects (Gatch et al. 2009; Winter 2009). For example, DMT, which is structurally similar to DiPT, also only partially substituted in LSD-trained rats (Gatch et al. 2009).

The purpose of this study was to further characterize the discriminative stimulus effects of the synthetic hallucinogen, DiPT. One reason for interest in DiPT is that the Drug Enforcement Agency has identified DiPT as a compound of concern due to increased street usage, and another is to find whether having auditory rather than visual effects also makes the discriminative stimulus effects of DiPT qualitatively different from those of other hallucinogens.

There were three goals for this experiment. The first goal was to evaluate whether DiPT can be trained as a discriminative stimulus and if so, to establish the dose effect. Secondly, the time course of the discriminative stimulus effects of DiPT was evaluated. Thirdly, because little is known about the behavioral effects of DiPT, the discriminative stimulus effects of DiPT were compared to those of a range of compounds comprised of different structural classes of hallucinogens and a psychostimulant. The effects of psychedelic compounds can be classified into three classes: hallucinogen, stimulant and other (Glennon 1999). Hallucinogens are further divided into three classes: simple tryptamines (indolealkylamines), ergolines and phenethylamines (see review by Nichols 2004). To test the effects of DiPT across all the categories, different commonly abused compounds that also represent each of the above mentioned classes were used: DMT (indolealkylamine), LSD (ergoline), DOM (phenethylamine hallucinogen), (+)-methamphetamine (phenethylamine psychostimulant) and MDMA (phenethylamine psychostimulant/hallucinogen).

Methods

Animals

Male Sprague–Dawley rats were obtained from Harlan Sprague–Dawley (Indianapolis, IN). All rats were housed individually and were maintained on a 12:12 light/dark cycle (lights on at 7:00AM). Body weights were maintained at 320–350 g by limiting food to 20 g/day

which included the food received during training sessions. Water was freely available in the home cages. All housing and procedures were in accordance with the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council 2003), and were approved by the University of North Texas Health Science Center Animal Care and Use Committee.

Drug discrimination procedures

Standard behavior-testing chambers (Coulbourn Instruments, Allentown, PA) were connected to IBM-PC compatible computers via LVB interfaces (MedAssociates, East Fairfield, VT). The computers were programmed in MED-PC IV (Med Associates, East Fairfield, VT) for the operation of the chambers and collection of data.

A group of 9 rats were trained to discriminate N,N-diisopropyltryptamine (DiPT; 5 mg/kg) from saline using a two-lever choice methodology. Food (45 mg food pellets; Bio-Serve, Frenchtown, NJ) was available under a fixed-ratio 10 schedule of reinforcement when responding occurred on the injection-appropriate lever. There were no consequences scheduled for incorrect responses. Of the nine rats that learned the discrimination task four of the rats were trained with drug as the cue on the right lever; five were trained with drug on the left lever. Training sessions occurred in a double alternating fashion (D-D-S-S-D, etc.), and tests were conducted between pairs of identical training sessions (i.e., between either two saline or two drug-training sessions).

During each training session, the rats received an intraperitoneal injection of either saline or DiPT. The training dose was 5 mg/kg with a 15-min pretreatment time. After the 15-min pretreatment time, the rats were placed in the experimental chamber. During the session, the rats could earn up to 20 food pellets by responding under an FR10 schedule of food presentation. If all 20 food pellets were delivered before the end of the 10-min response period, the house lights were turned off and responding had no scheduled consequences for the remainder of that response period. Animals received approximately 60 training sessions in total before use in any behavioral experiment. Animals were selected for use in experiments when they had achieved 85% injection-appropriate responding for both the first reinforcer and for the total session during nine of their last ten training sessions.

For testing, groups of at least six rats were administered each test drug. The ability of DMT, DOM, LSD and (+)-methamphetamine to substitute was tested in rats trained to discriminate DiPT from saline. A time course of DiPT was also measured. A repeated measures design was used, such that each rat was tested at all doses of the test compounds. Test sessions lasted for a maximum of 20 min to allow for potentially delayed effects of test compounds. In contrast with training sessions, both levers were active, such that ten consecutive responses on either lever led to reinforcement. Data were collected until 20 food pellets were obtained, or for a maximum of 20 min. Rats were tested only if they had achieved 85% injection-appropriate responding for both first reinforcer and total session on the two prior training sessions. At least 3 days elapsed between test sessions.

DiPT time course

To determine the time course of DiPT, the drug discrimination testing session was altered. The total session consisted of a maximum of 50 lever presses or 5 reinforcers or 5 minutes. In the control sessions, rats first received vehicle (0.9% saline) after a 15 minute pretreatment time and then placed in the behavior-testing chambers for testing. Upon completion the animals had a 10 minute period of time before administration of 5 mg/kg of DiPT. Subsequently, animals were placed in the behavior-testing chambers at 5, 15, 30, 60, 120 and 240 minutes post drug administration.

Drugs

(+)-Methamphetamine hydrochloride, (+)-lysergic acid diethylamide (+)-tartrate, (–)-2,5-dimethoxy-4-methylamphetamine hydrochloride, (±)3,4-methylenedioxymethamphetamine, N,N-dimethyltryptamine fumarate, and N,N-diisopropyltryptamine hydrochloride were provided by the National Institute on Drug Abuse. All drugs were dissolved in 0.9% saline and were administered i.p. in a volume of 1 ml/kg. Dose increments were based on 1/3 logs.

Data analysis

Drug discrimination data were expressed as the mean percentage of responses on the drug-appropriate lever for the total session data. Rates of responding were expressed as a function of the number of responses made divided by the total session time. Graphs for percent drug-appropriate responding (DAR) and response rate were plotted as a function of dose of test compound (log scale). Error bars show standard error of the mean. Full substitution was defined as 80% DAR and not statistically different from the training drug, and partial substitution as 40% and <80% DAR.

The potencies of test compounds that fully substituted were calculated by fitting straight lines to the individual dose–response data for each compound by means of TableCurve 2D (Jandel Scientific, San Rafael, CA). Straight lines were fitted to the linear portion of dose–effect curves, defined by doses producing 20% to 80% of the maximal effect, including not more than one dose producing <20% of the maximal effect and not more than one dose producing >80% of the maximal effect. Other doses were excluded from the analyses. The ED₅₀ values are expressed as the mean percent responding of the drug-appropriate lever per group ± standard error of the mean. Rates of responding were expressed as a function of the number of responses made divided by the total session time. Response rate data were analyzed by one-way, repeated measures analysis of variance. Effects of individual doses were compared to the appropriate control value using *a priori* contrasts. Criterion for significance was set *a priori* at $p < 0.05$.

Results

DiPT Discriminative Stimulus

DiPT (5 mg/kg, i.p.), when administered 15 min before testing, was successfully trained as a discriminative stimulus in 9 rats (Fig. 1). The rats needed an average (± standard error) of 55±4.9 sessions to reach criterion. Salivation was often observed following administration of the 5 mg/kg training dose throughout the training period. When training was completed, the time course of 5 mg/kg DiPT was evaluated and the dose-effect function of DiPT was established.

In the drug discrimination paradigm, DiPT (0.5 to 5 mg/kg) produced dose-dependent increases in DAR, with peak responding (99.5% DAR) following the training dose of 5 mg/kg (Fig 3). An ED₅₀ of 2.47±0.07 mg/kg was calculated. Response rates were not changed at any dose of DiPT.

Time Course

A single dose of DiPT (5 mg/kg, i.p.) increased DAR [$F(6,36)=21.125$, $p < 0.001$]. The onset of the discriminative stimulus effects of DiPT occurred within 5 minutes and the effects were gone within four hours (Fig. 2). Full DiPT-like effects (greater than 80% DAR) were seen at 5, 15 and 30 min after administration. DiPT-appropriate responding remained significantly different from control at 60 min (72.17% DAR) and 120 min (41.19% DAR)

following administration. DAR diminished to less than 1% by 240 min after administration. Response rates were not changed at any time point following administration of DiPT.

Similarly, a single dose of DMT (5 mg/kg, i.p.) increased DAR [$F(4,24)=9.875$, $p<0.001$]. The onset of the discriminative stimulus effects of DMT occurred within 5 minutes and the effects were gone within 1 hour (Fig. 2). Full DMT-like effects (greater than 80% DAR) were seen at 5 min after administration and remained significantly elevated from control 15 min (71.18% DAR) after administration. DMT decreased response rate [$F(4,24)=3.653$, $p=0.013$], with a significant depression observed only at 5 min following administration.

Substitution Testing

LSD ($ED_{50} = 0.023-0.085$ mg/kg), DOM ($ED_{50} = 0.22-0.133$ mg/kg), and (–)-MDMA ($ED_{50} = 2.48-0.04$ mg/kg) each fully substituted for the discriminative stimulus effects of DiPT (Fig 3). LSD produced a maximum of $99\pm0.5\%$ DiPT-appropriate responding following 0.05 and 0.1 mg/kg and decreased response rates only at the highest dose tested [$F(4,20)=8.432$, $p=0.004$]. DOM produced a maximum of $80\pm14\%$ DiPT-appropriate responding following 0.5 mg/kg and did not alter response rates. MDMA produced a maximum of $95\pm4\%$ DiPT-appropriate responding following 3 mg/kg and decreased response rates following 3 mg/kg [$F(5,30)=8.801$, $p=.001$].

DMT produced a maximum of $65\pm20\%$ DiPT-appropriate responding at 10 mg/kg. DMT dose-dependently decreased response rates [$F(5,40)=6.241$, $p=0.002$]. Higher doses were not tested due to suppression of responding. In contrast, (+)-methamphetamine (0.1-1 mg/kg) failed to produce significant levels of DiPT-appropriate responding, with maximal effects of 28% at 0.5 mg/kg. (+)-Methamphetamine did not significantly alter response rate at the doses tested. Higher doses of (+)-methamphetamine were not tested due to risk of toxicities.

Discussion

The discriminative stimulus effects of DiPT were evaluated in male Sprague Dawley rats. The rats learned to discriminate 5 mg/kg DiPT from saline and the discrimination was dose-dependent. The training dose for DiPT of 5 mg/kg was selected based on an earlier study in which 5 mg/kg produced maximal effects without rate suppression, and adverse effects occurred at higher doses of DiPT (Gatch et al. 2011). Transient salivation was observed in some animals starting at 5 mg/kg, suppression of motor activity at 10 mg/kg, and seizures were observed at 25 mg/kg. In the present study, salivation was often observed 15-20 min after administration of the 5 mg/kg training dose. The pretreatment time was based on peak locomotor effects of DiPT (Gatch et al. 2011). The time course of the discriminative stimulus effects indicated that 15 min was an appropriate length of time for observation of maximal effects. The discriminative stimulus effect of DiPT had a rapid onset (within 5 min) and diminished within 4 hours, which was substantially longer than that of DMT which is rapidly degraded by the enzyme monoamine oxidase type A (Buckholtz and Boggan 1977).

In the present study, DOM, LSD and MDMA fully substituted for the discriminative stimulus effects of DiPT, whereas DMT only partially substituted and (+)-methamphetamine failed to substitute for DiPT. Earlier work tested the discriminative stimulus effects of DiPT in separate groups of animals trained to discriminate LSD, DOM, DMT, MDMA and (+)-methamphetamine from saline (Gatch et al. 2011). The results of the cross-substitution were not completely symmetrical, which suggests that these compounds do not share completely overlapping mechanisms of action for their discriminative stimulus effects. Two compounds did produce comparable effects in the two studies, DOM and (+)-methamphetamine. DOM

fully substituted for the DiPT discriminative stimulus and DiPT fully substituted for the DOM discriminative stimulus. Similarly, (+)-methamphetamine failed to substitute for the discriminative stimulus effects of DiPT and DiPT failed to substitute in (+)-methamphetamine-trained animals. These results make sense, as DOM is primarily an agonist at the 5-HT_{2A} and 5-HT_{2C} receptors (Glennon 1988; Pierce and Peroutka 1989; Titeler et al. 1988) whereas (+)-methamphetamine has a primarily dopaminergic mechanism.

In contrast, DiPT fully substituted in rats trained to discriminate DMT (Gatch et al. 2011), but DMT produced only 65% DAR in rats trained to discriminate DiPT. This was unexpected, as DiPT and DMT have very similar structures. It is possible that higher doses of DMT may have fully substituted, but those doses produce complete suppression of responding, which precluded testing (data not shown). This notion is supported by findings that DMT produced a similar profile of cross-substitution as DiPT (Gatch et al. 2009). Full substitution occurred with LSD, DOM and MDMA in both DMT- and DiPT-trained animals, whereas (+)-methamphetamine failed to substitute. Conversely, both DMT (Gatch et al. 2009; Glennon 1986; Glennon et al. 1983) and DiPT (present study) fully substituted for DOM. DMT partially substituted for LSD (Appel et al. 1999; Gatch et al. 2009; Helsley et al. 1998; Jarbe 1980) as did DiPT (Gatch et al. 2011), and DMT failed to substitute for (+)-methamphetamine (Gatch et al. 2009) as did DiPT (Gatch et al. 2011). The only difference between DMT and DiPT was that DMT produced 50% DAR in MDMA-trained rats (Gatch et al. 2009), whereas DiPT produced only 19% DAR (Gatch et al. 2011). Since these two tryptamine compounds are structurally similar, it is not surprising that they shared a very similar profile. Previous studies suggest that DiPT and DMT, being structural analogues, may share similar mechanisms of action. DiPT and DMT inhibited transport at serotonin transporter (SERT) and vesicular monoamine transporter 2 (VMAT2) in relatively the same micromolar range at SERT (Gatch et al. 2011; Nagai et al. 2007; Cozzi et al. 2009). DiPT had a slightly greater affinity at VMAT2 than DMT at 93 ± 6.8 and 19 ± 3.1 μ M. (Cozzi et al. 2009).

In the present study, LSD fully substituted in rats trained to discriminate DiPT, but DiPT only partially substituted in rats trained to discriminate LSD (Gatch et al. 2011). DiPT decreased response rates, so that higher doses could not be tested, but a plateau was observed, suggesting that higher doses may not have produced higher levels of LSD-appropriate responding. Finally, MDMA fully substituted in rats trained to discriminate DiPT, which was somewhat unexpected as DiPT produced little or no DAR in rats trained to discriminate MDMA (Gatch et al. 2011). In contrast, 3 mg/kg MDMA, which is twice the size of the MDMA training dose, fully substituted in rats trained to discriminate DMT, but DMT produced dose-dependent increases in DAR to about 50% in rats trained to discriminate MDMA (Gatch et al. 2009).

Taken together, DiPT shares discriminative stimulus properties with serotonergic hallucinogens but not dopaminergic psychostimulants, which suggests that DiPT may have a similar stimulus properties as LSD, DOM and DMT. However, the lack of symmetrical cross-substitution with DMT shows that the two compounds may have at least somewhat distinctive stimulus effects. The putative auditory effects of DiPT do not appear to produce discriminative stimulus effects distinguishable from those serotonin-mediated hallucinogens known to produce visual effects.

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Fig. 1.

Learning curve showing the acquisition of the discrimination between DiPT (*closed squares*) and the saline vehicle (*open squares*). The *y*-axis shows percentage of responding on the DiPT-appropriate lever over 30 saline- and 30 drug-training sessions. *Error bars* show standard error of the mean. Each point represents the average of 9 rats.

Fig. 2.

Time course of the discriminative stimulus effects of the 5 mg/kg training dose of N,N-diisopropyltryptamine (DiPT, *squares*) and N,N-dimethyltryptamine (DMT, *circles*). The y-axis shows percentage of responding on the drug-appropriate lever over a time period ranging from 5 minutes to 240 minutes post injection. Each point represents the average of 7 rats.

Fig. 3.

Cross-substitution of DMT, DOM, LSD and (+)-methamphetamine. *Top panel* shows drug-appropriate responding of the test compounds in DiPT-trained rats. *Closed squares*-LSD, *hexagon*-(+)-methamphetamine, *triangle*-DiPT dose response, *open diamond*-DOM, *closed diamond*-MDMA, *open squares*-DMT. (*Bottom panel* show rate of responding in responses per second. Unless otherwise noted (by numbers in parentheses): DMT N=9, DOM and (+)-methamphetamine N=7, LSD N=6. *Indicates points different from the vehicle control. *Meth* (+)-methamphetamine

Table 1

Peak effects for cross substitution between DiPT and other psychoactive compounds. Data for substitution by DiPT in rats trained to discriminate DMT, DOM, LSD, MDMA and (+)-methamphetamine are taken from Gatch et al. (2011).

Comparison Compounds	Substitution by DiPT		Substitution in DiPT-trained rats	
	%DAR $\pm$ sem	Dose (mg/kg)	%DAR $\pm$ sem	Dose (mg/kg)
DMT	82 $\pm$ 16	5	65 $\pm$ 20	10
DOM	83 $\pm$ 17	5	80 $\pm$ 14	0.5
LSD	68 $\pm$ 20	5	99 $\pm$ 0.5	0.05
MDMA	19 $\pm$ 16	5	95 $\pm$ 5	3
(+)-methamphetamine	16 $\pm$ 14	5	29 $\pm$ 1	0.5