Discriminative stimulus effects of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) in rhesus monkeys

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Abbreviations: fixed ratio, FR; serotonin, 5-HT; 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane, DOM; (+)-lysergic acid diethylamide, LSD; 2,5-dimethoxy-4-(n)-propylthiophenethylamine, 2C-T-7

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Abstract

Discriminative stimulus effects of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) and related drugs have been studied extensively in rodents, although the generality of those findings across species is not known. The goals of this study were to see whether monkeys could discriminate DOM and to characterize the DOM discriminative stimulus by studying a variety of drugs, including those with hallucinogenic activity in humans. Four rhesus monkeys discriminated between 0.32 mg/kg (s.c.) of DOM and vehicle after an average of 116 (range=85-166) sessions while responding under a fixed ratio (FR) 5 schedule of stimulus shock termination. Increasing doses of DOM occasioned increased responding on the drug lever with the training dose occasioning DOM-lever responding for up to 2 hrs. The serotonin (5-HT)\textsubscript{2A/2C} receptor antagonists ritanserin and ketanserin, the 5-HT\textsubscript{2A} receptor antagonist MDL100907 and its stereoisomer MDL100009, but not haloperidol, completely blocked the discriminative stimulus effects of DOM. Quipazine as well as several drugs with hallucinogenic activity in humans, including (+)lysergic acid diethylamide (LSD), (-)DOM and 2,5-dimethoxy-4-(n)-propylthiophenethylamine (2C-T-7), occasioned DOM-lever responding. The \textit{kappa} opioid receptor agonists U-50488 and salvinorin A (a hallucinogen) did not exert DOM-like effects and neither did ketamine, phencyclidine, amphetamine, methamphetamine, cocaine, morphine, yohimbine, fenfluramine, 8-OH-DPAT or N-0434. These data confirm in non-human primates a prominent role for 5-HT\textsubscript{2A} receptors in the discriminative stimulus effects of some drugs with hallucinogenic activity in humans. The failure of another drug with hallucinogenic activity (salvinorin A) to substitute for DOM indicates that different classes of hallucinogens exert qualitatively different discriminative stimulus effects in non-humans.
Introduction

Drug discrimination procedures have been used to study a wide variety of drugs including the well-known hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM; Glennon et al., 1983a; Silverman and Ho, 1980). Several studies have established stimulus control with DOM in rats and examined the structure-activity relationships for various drugs acting on serotonergic (5-HT) systems (for reviews, see Glennon et al., 1983b; Glennon, 1988; Winter et al., 1999). DOM exerts pharmacologically-selective stimulus effects that appear to be due to actions at a specific type of 5-HT receptor and it is possible that this discrimination procedure is related to the hallucinogenic effects of drugs (Glennon, 1988). Collectively these studies in rats have demonstrated a predominant role for 5-HT$_{2A}$ receptors in the discriminative stimulus of DOM (Glennon et al., 1983a; Glennon and Hauck, 1985). DOM also binds with a somewhat lower affinity to 5-HT$_{2C}$ receptors (Titeler et al. 1988) and there is some evidence as well for a role of 5-HT$_{2C}$ receptors in the discriminative stimulus effects of DOM in rats (Fiorella et al. 1995a).

DOM and related drugs have also been studied in non-human primates, but almost exclusively in animals discriminating drugs from other (non-hallucinogenic) classes (e.g. Woolverton and English, 1997); there is only one report of non-human primates trained to discriminate a prototypic hallucinogen (lysergic acid diethylamide [LSD]; Nielsen, 1985). Thus, relatively little is known about the discriminative stimulus effects of DOM, LSD and related drugs in non-human primates, despite the recognized value of non-human primates in drug abuse research (e.g., Weerts et al., 2007) and the need for cross-species comparisons to establish the generality of drug discrimination data.

For many drugs discriminative stimulus effects are very consistent across species and testing conditions, although notable differences have been reported. For example, some compounds with affinity for 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors mimic the discriminative stimulus effects of the 5-HT$_{1A}$ receptor agonist 8-OH-DPAT in pigeons (Barrett and Gleeson, 1992) and not in rats (Cunningham et al. 1987). Lisuride and eltoprazine occasion high levels of 8-OH-DPAT-appropriate responding in pigeons and not in rats (Kleven and Koek, 1998). Metaphit, a derivative of phencyclidine, has phencyclidine-like discriminative stimulus
effects in pigeons and not in rhesus monkeys (Koek et al., 1986). Zolpidem substitutes fully for the pentobarbital discriminative stimulus in rhesus monkeys (Rowlett et al., 1997), but only partially for pentobarbital in rats. Moreover, the effects of zolpidem in humans (Rush et al., 1997) parallel results obtained in non-human primates, suggesting that for some drugs the predictive relationship between discriminative stimulus effects might be greater between non-human primates and humans, as compared to rodents and humans. In mice both 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors appear to play a role in the discriminative stimulus effects of 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI; Smith et al., 2003), whereas in rats there is no evidence for a role of 5-HT$_{2C}$ receptors in the discriminative stimulus effects of DOI (Schreiber et al., 1994). In monkeys discriminating LSD, ketanserin and pirenperone fail to antagonize the discriminative stimulus of LSD (Nielsen, 1985); however, in rats discriminating LSD, ketanserin and pirenperone completely antagonize LSD (Cunningham and Appel, 1987). Thus, it is not known to what extent the discriminative stimulus effects of DOM, LSD and related drugs are different among species; consequently, the predictive validity of discrimination procedures in non-human species for drug effects in humans (e.g., hallucinations) has yet to be confirmed across species.

The present study had two goals, the first of which was to determine whether monkeys could be trained to discriminate DOM in a standard two-lever procedure. Because reliable discriminative control was established with DOM, a second goal was to characterize the DOM discriminative stimulus in monkeys by conducting substitution and antagonism studies with compounds that had been studied previously in rats discriminating DOM and also with compounds that had not been studied previously in a DOM discrimination procedure. Non-human primates have been used extensively to study the behavioral effects of many known and suspected drugs of abuse (Weerts et al., 2007), although relatively little research in non-human primates has focused on drugs with hallucinogenic activity in humans.
Methods

Subjects

Four adult rhesus monkeys (two males, two females) weighing between 4 and 8 kg were housed individually in stainless steel cages where they had unlimited access to water. Monkeys received primate chow (Harlan Teklad High Protein Monkey Diet, Madison, WI), fresh fruit, and peanuts after daily sessions in quantities sufficient to maintain normal, age- and gender-appropriate weights. Monkeys were maintained on a 14-h/10-h light/dark cycle and were drug-naïve prior to the beginning of this study. The animals used in this study were maintained in accordance with the Institutional Animal Care and Use Committee, The University of Texas Health Science Center at San Antonio, and with the 1996 Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animals Resources on Life Sciences, National Research Council, National Academy of Sciences).

Apparatus

During experimental sessions, subjects were seated in commercially-available chairs (Model R001, Primate Products, Miami, FL) that were placed in ventilated, sound-attenuating chambers equipped with stimulus lights and response levers. The feet of monkeys were placed in shoes that were mounted to the front of the chair and equipped with brass electrodes to which a brief (250 ms, 3 mA) electric shock could be delivered from an a.c. generator. Experiments were controlled and data recorded with a microprocessor and a commercially available interface (Med Associates Inc., East Fairfield, VT).

Procedure

Initially monkeys were trained to press either of the two levers for banana-flavored food pellets (300 mg, Bio-Serv, Frenchtown, NJ). After the monkeys responded reliably for food (i.e., received 50 pellets in five consecutive sessions) the stimulus-shock termination schedule was introduced and discrimination training commenced with DOM and saline. Training sessions were conducted daily with drug (D) or saline.
(S) administered according to a double-alternating sequence as follows: DDSSDD…. Daily training sessions began with a 30-min timeout period, during which stimulus lights were not illuminated and responding had no programmed consequence, followed by a 10-min response period, during which stimulus lights were illuminated above each lever and monkeys could extinguish the stimulus lights and postpone the shock schedule for 30 s by responding five times consecutively (fixed ratio [FR] 5) on the lever designated correct by an injection (s.c.) administered during the first minute of the cycle (i.e., right lever after saline and left lever after 0.32 mg/kg DOM for two monkeys; lever designations were the opposite for the other two monkeys). Incorrect responses reset the FR requirement on the correct lever. Failure to satisfy the FR requirement within 30 s of illumination of the stimulus lights resulted in the delivery of a brief shock every 30 s until the response requirement was satisfied. The cycle ended after 40 min (30-min timeout followed by 10-min response period) or after delivery of four shocks, whichever occurred first.

Injections were made s.c. in the back during the first minute of the timeout. Initially, monkeys had to satisfy the following criteria for 5 consecutive or 6 of 7 sessions: at least 80% of the total responses on the correct lever; and fewer than 5 responses on the incorrect lever prior to completion of the FR on the correct lever. Thereafter, monkeys typically were tested every third day provided that the testing criteria were satisfied during intervening training sessions. If monkeys failed to satisfy these criteria, then training continued until the criteria were satisfied for two consecutive sessions.

Test sessions were identical to training sessions except that 5 consecutive responses on either lever postponed scheduled shock and different doses of DOM and other drugs were administered during the timeout. Time course studies were conducted by administering a single dose of drug at various times before the test session. Antagonism studies were conducted by administering a single dose of an antagonist before the administration of DOM (0.32 mg/kg) or quipazine (3.2 mg/kg). Except for time course studies when an antagonist was administered at different times prior to the session, antagonists were administered 5 minutes before the timeout period. For pretreatment times greater than 15 minutes, drug was administered in the home cage. Antagonism studies used the selective 5-HT2A receptor antagonist MDL 100907, its
stereoisomer MDL100009, the 5-HT receptor antagonists ketanserin and ritanserin, and the non-selective dopamine receptor antagonist haloperidol. The order of testing varied non-systematically among monkeys.

**Data Analyses**

Drug discrimination data are expressed as the percentage of total responses on the DOM-associated lever averaged among monkeys (± 1 SEM) and plotted as a function of dose or time. When a monkey responded at a rate that was less than 20% of its vehicle control rate, discrimination data from that test were not included in the average, although the response rate data were included in the group average. Rate of lever pressing on both levers is plotted in responses per second and reported as the average ± 1 SEM for all tests. For drugs that occasioned at least 80% responding on the DOM-associated lever, the dose required to produce 50% DOM-lever responding was estimated (ED$_{50}$ [95% confidence limit]) using linear regression. Doses of antagonists to decrease DOM-lever responding to 50% (AD$_{50}$ [95% confidence limit]) were estimated using linear regression.

**Drugs**

Compounds provided by NIDA (Research Technology Branch, Rockville, MD) were as follows: 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) and its levo-isomer (-) DOM; 2,5-dimethoxy-4-(n)-propylthiophenethylamine (2C-T-7); lysergic acid diethylamide (LSD); salvinorin A; U-50488 hydrochloride, morphine sulfate; cocaine hydrochloride; d-amphetamine sulfate; methamphetamine hydrochloride; and phencyclidine hydrochloride. DOM was also provided by Alcon Research, Ltd. (Fort Worth, TX). Compounds that were purchased from Sigma-Aldrich (St. Louis, MO) were as follows: (±)-2-(N-phenethyl-N-1'-propyl)amino-5-hydroxytetralin (PPHT) hydrochloride (N-0434); quipazine maleate; haloperidol; yohimbine hydrochloride; fenfluramine hydrochloride; ketanserin tartrate; ritanserin; and 8-hydroxy-2-(dipropylamino)tetralin hydrobromide (8-OH-DPAT). Ketamine hydrochloride was purchased as a commercially-available solution (Vetus Animal Health, MFA Inc., Columbia, MO). The selective 5-HT$_{2A}$ receptor antagonist (+/-)2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol] (MDL 100907) and its optical
isomer MDL100009 were by KCR. With the following exceptions, all compounds were dissolved in sterile
0.9% saline: MDL100907 and MDL100009 were dissolved in 20% DMSO (v/v); haloperidol was first
dissolved with a few drops of glacial acetic acid then diluted in saline and buffered to pH 6.5-7.0. Doses are
expressed as the forms indicated above and compounds were injected s.c. in a volume of 0.1-1.0 ml.
Results

Responding by monkeys was under adequate stimulus control for testing after an average of 116 (range=85-166) training sessions. Saline and small doses of DOM occasioned responding predominantly on the saline-associated lever, whereas larger doses of DOM increased responding on the DOM-associated lever responding (ED$_{50}$ = 0.124 [95% confidence limits = 0.021, 0.227] mg/kg; Figure 1, upper left panel). DOM also decreased rate of responding with the largest dose (0.32 mg/kg) decreasing the average rate to 52% of the saline control rate (Figure 1, lower left panel). The discriminative stimulus effects of 0.32 mg/kg DOM were evident 15 min and were maximal 30 min after administration (Figure 1, upper right panel). Sixty min after administration, monkeys responded on average 81% on the DOM lever; thereafter, the discriminative stimulus effects of DOM decreased in a time-related manner with only 13% DOM-lever responding 240 min after administration. In parallel to this time-related decrease in discriminative stimulus effects was a time-related recovery in response rate (Figure 1, compare upper and lower right panels).

LSD, (-)DOM, 2C-T-7 and quipazine dose-dependently increased responding on the DOM lever (Figure 2, upper panel) with the largest dose of each compound occasioning more than 90% DOM-lever responding (LSD ED$_{50}$ = 0.008 mg/kg [0.003, 0.012]; (-)DOM ED$_{50}$ = 0.100 mg/kg [0.054, 0.145]; 2C-T-7 ED$_{50}$ = 0.113 mg/kg [0.020, 0.206]; and quipazine ED$_{50}$ = 1.59 mg/kg [0.82, 2.37]). These compounds varied in their effects on response rate with dose-related decreases in responding for 2C-T-7 and no clearly dose-related effects on rate for the other three compounds (Figure 2, lower panel).

Salvinorin A and U-50488 occasioned predominantly saline-lever responding up to doses that markedly decreased or eliminated responding (Table 1). Phencyclidine and ketamine occasioned some (average maximum of 45 and 38%, respectively) responding at doses of each that markedly decreased rate of responding (Table 1). Amphetamine, methamphetamine, cocaine, and morphine occasioned exclusively or predominantly saline-lever responding up to the largest doses that could be tested safely on these monkeys (Table 1). Some doses of methamphetamine, amphetamine and cocaine increased rate of responding, with maximum increases to 167%, 179% and 159% of the saline control rate, respectively (Table 1). Morphine
did not markedly affect response rate. N-0434, yohimbine, and fenfluramine also occasioned predominantly saline-lever responding (Table 1). N-0434 dose-dependently increased rate of responding, with the largest dose tested (0.178 mg/kg) increasing rate to 171% of the saline control rate. Yohimbine had no clear effect on response rate at the doses tested while 3.2 and 10 mg/kg fenfluramine markedly decreased response rate to 44% and 37% of the saline control rate, respectively (Table 1). Larger doses of yohimbine and fenfluramine were not tested. After receiving 8-OH-DPAT up to a dose that nearly eliminated responding (0.32 mg/kg), monkeys responded exclusively on the saline-associated lever.

MDL 100907, ketanserin, ritanserin and MDL100009 each dose-dependently attenuated the discriminative stimulus effects of the training dose (0.32 mg/kg) of DOM (Figure 3, upper panel), with the largest dose of each decreasing DOM-lever responding to less than 10% (MDL100907 AD50 = 0.002 mg/kg [0.001, 0.004]; ketanserin AD50 = 0.075 mg/kg [0.029, 0.120]; ritanserin AD50 = 0.168 mg/kg [0.042, 0.338]; and MDL100009 AD50 = 0.343 mg/kg [0.193, 0.491]). Haloperidol had no effect on the discriminative stimulus effects of 0.32 mg/kg DOM up to a dose (0.32 mg/kg) that nearly eliminated responding.

MDL 100907 antagonized the discriminative stimulus effects of 3.2 mg/kg DOM within 5 minutes of its administration and continued to do so in some monkeys for several hours. This antagonism decreased slightly when MDL 100907 was administered 2 hrs or more before DOM and was no longer evident 8 hrs after administration (Figure 4).
Discussion

Although the discriminative stimulus effects of drugs that have hallucinogenic activity in humans have been studied extensively in rodents, these drugs have been studied much less in non-human primates and other species. In fact, there is only a single published report (Nielsen, 1985) of non-human primates being trained to discriminate a prototypic drug with well-established hallucinogenic activity in humans (e.g., LSD). Thus, the first goal of this study was to see whether monkeys could be trained to discriminate the well-known hallucinogen DOM. To that end, all four monkeys reliably discriminated between 0.32 mg/kg of DOM and vehicle after an average of 116 training sessions, which is similar to the training needed to establish stimulus control with other drugs in monkeys (e.g., Gerak et al., 1996). The discriminative stimulus effects of DOM remained stable throughout the course of these studies (two years) and they were time- and dose-related, with maximal effects occurring within 30 min of s.c. administration and no effects evident 240 min after administration. Despite very rapid penetration of brain (Eckler et al., 2001) after systemic administration, the discriminative stimulus effects of DOM take longer to emerge in rats. And in humans DOM is reported to have a very long duration of action (14-20 hr) after oral administration (Shulgin and Shulgin, 1991). Differences in onset and duration of action of DOM among species could reflect differences in metabolic activity. Nevertheless, this study clearly demonstrates that non-human primates readily discriminate DOM.

The results of studies that were conducted largely with rodents implicate 5-HT mechanisms in the behavioral effects, including the discriminative stimulus effects, of DOM and related compounds (Glennon et al., 1983a; Glennon and Hauck, 1985). In the current study drugs with agonist activity at 5-HT₂ receptors, including LSD, (-)DOM, 2C-T-7 and quipazine occasioned responding on the DOM-associated lever, whereas drugs from other classes, including drugs that do not produce hallucinations in humans, did not occasion responding on the DOM lever. With the exception of quipazine, for which there is relatively little data from humans, it appears as though only drugs with pronounced hallucinogenic effects in humans share discriminative stimulus effects with DOM in rhesus monkeys. This is the first report showing that 2C-T-7
shares discriminative stimulus effects with DOM in rhesus monkeys and these results might be relevant to the abuse of 2C-T-7 (Schifano et al., 2005); in rats LSD substitutes fully for DOM and only partially for 2C-T-7 (Fantegrossi et al., 2005), suggesting that there might be significant differences among these drugs across species.

In general, the discriminative stimulus effects of drugs are very similar across species and across testing conditions. However, tests with yohimbine and fenfluramine, neither of which is reported to produce hallucinations in humans, have yielded inconsistent effects in rats discriminating a prototypic hallucinogen. For example, in rats yohimbine shares discriminative stimulus effects with LSD in some (Colpaert, 1984) and not other studies (Fiorella et al. 1995a). Also in rats, fenfluramine substitutes fully for DOM (Glennon 1988) and only partially for LSD (Winter, 1980). Up to the largest doses that could be studied safely, neither yohimbine nor fenfluramine had DOM-like discriminative stimulus effects on monkeys. It is not clear whether these differences in substitution profiles between rats and monkeys are due to procedural differences (e.g., training dose) or to differences in the qualitative features of the discriminative stimulus effects of 5-HT drugs across species. However, these results underscore the importance of systematically examining the same drugs across species and in relationship to their effects in humans in order to ascertain conditions in the preclinical laboratory that best predict effects in humans.

Up to doses that had other behavioral effects, pharmacologically-unrelated drugs did not substitute for DOM. For example, amphetamine, methamphetamine and cocaine all increased rates of responding under the schedule of stimulus-shock termination without occasioning DOM-lever responding. Similarly, the dopamine D2/D3 receptor agonist N-0434 that increases responding in the fixed-interval component of a multiple schedule in squirrel monkeys (Bergman et al., 1995) also markedly increased response rate in rhesus monkeys responding under a FR schedule. The selective 5-HT<sub>1A</sub> receptor agonist 8-OH-DPAT did not occasion DOM-lever responding while dose-dependently decreasing responding. That the noncompetitive NMDA antagonists ketamine and phencyclidine occasioned some, although only partial, DOM-lever responding is consistent with other studies showing partial substitution for and enhancement of the DOM
discriminative stimulus in rats (Winter et al., 2000). The mechanism by which NMDA antagonists and 5-HT agonists interact is not clear (Rabin et al., 2000), although with regard to drug discrimination data in particular it has been suggested that NMDA antagonists might non-selectively disrupt discrimination performance (e.g., Jackson et al., 1992).

MDL 100907 is an antagonist at 5-HT receptors with greater than 100-fold selectivity for 5-HT$_{2A}$ receptors ($K_I=0.85$ nM) as compared to 5-HT$_{2C}$ receptors ($K_I=88$ nM; Kehne et al. 1996). MDL 100907 is more than 1200 times more potent in antagonizing 5-HT-induced $[^{3}H]$inositol phosphate accumulation in cell transfected with 5-HT$_{2A}$ receptors, as compared to those transfected with 5-HT$_{2C}$ receptors, and it potently blocks 5-HT$_{2A}$ receptor agonist-induced head twitches mice (Kehne et al., 1996). Direct evidence for the role of 5-HT$_{2A}$ receptors in the discriminative stimulus effects of DOM in rhesus monkey was provided by results showing that MDL 100907 completely antagonized the discriminative stimulus effect of DOM. Although reportedly inactive under some conditions (e.g., Arvanov and Wang, 1998), the optical isomer of MDL100907 (MDL100009) also antagonized DOM being 142-fold less potent than MDL100907. The duration of action of MDL100907 was at least 4 hr in monkeys, which is similar to its duration of action in rats (Kehne et al., 1996) and, perhaps, shorter than its duration of action in humans (Gründer et al., 1997). This extended duration of action might be particularly useful for antagonism studies in which cumulative doses of agonists are administered after an acute administration of MDL100907.

Other studies with rats have shown that a variety of compounds with 5-HT$_2$ receptor antagonist actions, including ketanserin, pirenperone, LY-53857 and CP-52215, antagonize the discriminative stimulus effects of DOM and R-DOI and that pirenperone also blocks the DOM-like discriminative stimulus effects of quipazine (Glennon et al., 1983a; Glennon and Hauck, 1985). Ritanserin and ketanserin also dose-dependently antagonized the discriminative stimulus effect of DOM in monkeys, confirming similar antagonism of DOM with these drugs in rats (Glennon et al., 1983a, Glennon and Hauck, 1985). Consistent with results obtained in rats (Fiorella et al. 1995b), the dopamine receptor antagonist haloperidol had no effect on the DOM discriminative stimulus. Together with a substantial amount of data obtained with rats,
these data obtained with rhesus monkeys clearly demonstrate a prominent role for 5-HT$_{2A}$ receptors in the discriminative stimulus effects of DOM and related drugs. It is not clear whether other 5-HT receptor subtypes also might contribute to the DOM discriminative stimulus in monkeys, as appears to be the case in rats (e.g., Fiorella et al., 1995a).

Salvinorin A, from *Salvia divinorum*, has been used for many years in traditional religious ceremonies of the Mazatec culture in southern Mexico (Siebert, 1994). Salvinorin A is a potent and selective kappa opioid receptor agonist (Roth et al., 2002) that shares discriminative stimulus effects with prototypic kappa receptor agonists, including U69,593, in rhesus monkeys (Butelman et al., 2004). In humans, the subjective effects of salvinorin A are reported to be similar to other well-known hallucinogens such as LSD (Gonzalez et al, 2006), although other measures of subjective effects (e.g., LSD and PCAG subscales of the Addiction Research Center Inventory) indicate a greater similarity between salvinorin A and drugs with kappa agonist activity (Arasteh et al., 1999). In monkeys, salvinorin A and the prototypic kappa opioid receptor agonist U-50488 failed to occasion responding on the DOM-associated lever, up to doses that markedly decreased responding. That a drug with pronounced hallucinogenic activity in humans fails to exert DOM-like discriminative stimulus effects in monkeys indicates either that the qualitative (subjective) effects of hallucinogens vary significantly or that drug discrimination procedures in non-humans are not related to and therefore not directly predictive of hallucinogenic activity in humans. This negative finding with salvinorin A confirms the high degree of pharmacologic selectivity of the DOM discrimination for 5-HT (e.g., 5-HT$_{2A}$) receptor mechanisms.

In summary, this study established DOM as a discriminative stimulus in rhesus monkeys and characterized the pharmacologic profile of the DOM discriminative stimulus. The results confirm a prominent role for 5-HT$_{2A}$ receptor mechanisms in the discriminative stimulus effects of DOM and further suggest that different classes of hallucinogens (e.g., some kappa opioid agonists and 5-HT agonists) exert qualitatively different discriminative stimulus effects in non-humans. These results provide the first direct evidence for a high degree of concordance in the discriminative stimulus effects of prototypic hallucinogens.
between rodents and non-human primates. Given the value of non-human primates in drug abuse research
(Weerts et al., 2007) this procedure can be used to systematically explore the relationship between agonism
at different 5-HT receptors and hallucinogenic activity.

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Footnotes

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Legends for Figures

**Figure 1.** Discriminative stimulus and rate effects of DOM in rhesus monkeys. Each point represents the average (± SEM) of 4 monkeys. Ordinates: upper panels, average percentage of responses of the DOM-associated lever; lower panels, average rate of responding in response per second. Abscissae: left panels: dose in mg/kg body weight; right panels, time in min after administration of the training dose (0.32 mg/kg) of DOM. Points above “V” indicate saline vehicle.

**Figure 2.** Discriminative stimulus and rate effects of LSD, (-)DOM, 2C-T-7 and quipazine. See Figure 1 for other details.

**Figure 3.** Antagonism of the discriminative stimulus of 0.32 mg/kg of DOM by MDL 100907, ketanserin, ritanserin, MDL100009 and lack of antagonism by haloperidol. See Figure 1 for other details.

**Figure 4.** Time-course of antagonism by MDL100908 of 0.32 mg/kg of DOM. See Figure 1 for other details.
Table 1. Discriminative stimulus and rate effects of drugs in monkeys discriminating between saline and 0.32 mg/kg of DOM.

<table>
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<tr>
<th>Compound</th>
<th>Dose (mg/kg)</th>
<th>% Drug + SEM</th>
<th>Rate + SEM (Response/second)</th>
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Table 1 (continued)

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n.d. = not determined
Figure 1

% DOM-lever responding

Rate (Response/second)

Dose (mg/kg) DOM

Time (min) after 0.32 mg/kg DOM
Figure 2

% DOM-lever responding

- LSD
- (-) DOM
- 2C-T-7
- Quipazine

Rate (Response/second)

0.0 0.5 1.0 1.5 2.0

0.001 0.003 0.01 0.032 0.32 1.0 3.2

Dose (mg/kg)
Figure 3

% DOM-lever responding

Rate (Response/second)

MDL100907
Haloperidol
Ketanserin
Ritanserin
MDL100009

Dose (mg/kg)