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Discriminative Stimulus Effects of 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane in Rhesus Monkeys

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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. DOM and vehicle after an average of 116 (range = 85–166) sessions while responding under a fixed ratio 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 h. The serotonin (5-HT)$_{2A/2C}$ receptor antagonists ritanserin and ketanserin, the 5-HT$_{2A}$ receptor antagonist (+)2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol] (MDL100907), and its (−)stereoisomer MDL100009 [(−)2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol], 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, (−)DOM, and 2,5-dimethoxy-4-(*n*)-propylthiophenethylamine (2C-T-7), occasioned DOM-lever responding. The κ-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-hydroxy-2-(dipropylamino)tetralin hydrobromide (8-OH-DPAT), or (±)-2-(*N*-phenethyl-*N*-1′-propyl)amino-5-hydroxytetralin hydrochloride (N-0434). These data confirm in nonhuman primates a prominent role for 5-HT$_{2A}$ 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 nonhumans.

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$_{2C}$ re-

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ABBREVIATIONS: DOM, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane; 8-OH-DPAT, 8-hydroxy-2-(dipropylamino)tetralin hydrobromide; FR, fixed ratio; 5-HT, serotonin; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; LSD, (+)lysergic acid diethylamide; 2C-T-7, 2,5-dimethoxy-4-(*n*)-propylthiophenethylamine; N-0434, (±)-2-(*N*-phenethyl-*N*-1′-propyl)amino-5-hydroxytetralin hydrochloride; MDL100907, (+)2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]; MDL100009, (−)2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]; U50488, *trans*-(1*R*,2*R*)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-benzeneacetamine hydrochloride; LY-53857, 6-methyl-1-(1-methylethyl)-ergoline-8-carboxylic acid 2-hydroxy-1-methylpropyl ester maleate; CP-52215, 8-fluoro-5-(4-fluorophenyl)-2-(4-(4-fluorophenyl)-4-hydroxybutyl)-1*a*,2,3,4,4*a*,5-hexahydro-1*H*-pyrido[4,3-b]indole hydrochloride; U69,593, (5α,7α,8β)-(−)-*N*-methyl-*N*-7-(1-pyrrolidinyl)-1-oxaspiro(4,5) dec-8-yl) benzeneacetamide.

ceptors (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 nonhuman primates but almost exclusively in animals discriminating drugs from other (nonhallucinogenic) classes (e.g., Woolverton and English, 1997); there is only one report of nonhuman 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 nonhuman primates, despite the recognized value of nonhuman 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 and Woolverton, 1997) but only partially for pentobarbital in rats. Moreover, the effects of zolpidem in humans (Rush et al., 1997) parallel results obtained in nonhuman primates, suggesting that, for some drugs, the predictive relationship between discriminative stimulus effects might be greater between nonhuman primates and humans 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 nonhuman 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. Nonhuman 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 nonhuman primates has focused on drugs with hallucinogenic activity in humans.

Materials and 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 14/10-h light/dark cycle and were drug-naive before 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 Institute of Laboratory Animal Resources (1996).

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 alternating current generator. Experiments were controlled, and data were 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 1st min 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 1st min of the timeout. Initially, monkeys had to satisfy the following criteria for five consecutive or six of seven sessions: at least 80% of the total responses on the correct lever and fewer than five responses on the incorrect lever before completion of the FR on the correct lever. Thereafter, monkeys typically were tested every 3rd day provided that the testing criteria were satisfied during intervening training sessions. If monkeys failed to satisfy these criteria, training continued until the criteria were satisfied for two consecutive sessions.

Test sessions were identical to training sessions, with the exception that five 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). With the exception of time course

studies when an antagonist was administered at different times before the session, antagonists were administered 5 min before the timeout period. For pretreatment times greater than 15 min, drug was administered in the home cage. Antagonism studies used the selective 5-HT_{2A} receptor antagonist MDL100907, its stereoisomer MDL100009, the 5-HT receptor antagonists ketanserin and ritanserin, and the nonselective dopamine receptor antagonist haloperidol. The order of testing varied nonsystematically among monkeys.

Data Analyses. Drug discrimination data are expressed as the percentage of total responses on the DOM-associated lever averaged among monkeys (±1 S.E.M.) 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 S.E.M. 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 National Institute of Drug Abuse (Research Technology Branch, Rockville, MD) were as follows: 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: N-0434; quipazine maleate; haloperidol; yohimbine hydrochloride; fenfluramine hydrochloride; ketanserin tartrate; ritanserin; and 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 MDL100907 and its optical isomer MDL100009 were provided by K.C.R. With the following exceptions, all compounds were dissolved in sterile 0.9% saline. MDL100907 and MDL100009 were dissolved in 20% dimethyl sulfoxide (v/v); haloperidol was first dissolved with a few drops of glacial acetic acid and then diluted in saline and buffered to pH 6.5 to 7.0. Doses are expressed as the forms indicated above, and compounds were injected s.c. in a volume of 0.1 to 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) (Fig. 1, top left). 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 (Fig. 1, bottom left). The discriminative stimulus effects of 0.32 mg/kg DOM were evident 15 min and were maximal 30 min after administration (Fig. 1, top right). 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 (Fig. 1, compare top and bottom right panels).

LSD, (−)DOM, 2C-T-7, and quipazine dose-dependently increased responding on the DOM lever (Fig. 2, top) 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 (Fig. 2, bottom).

Salvinorin A and U-50488 occasioned predominantly saline-lever responding up to doses that markedly decreased or eliminated responding (Table 1). Phencyclidine and ke-

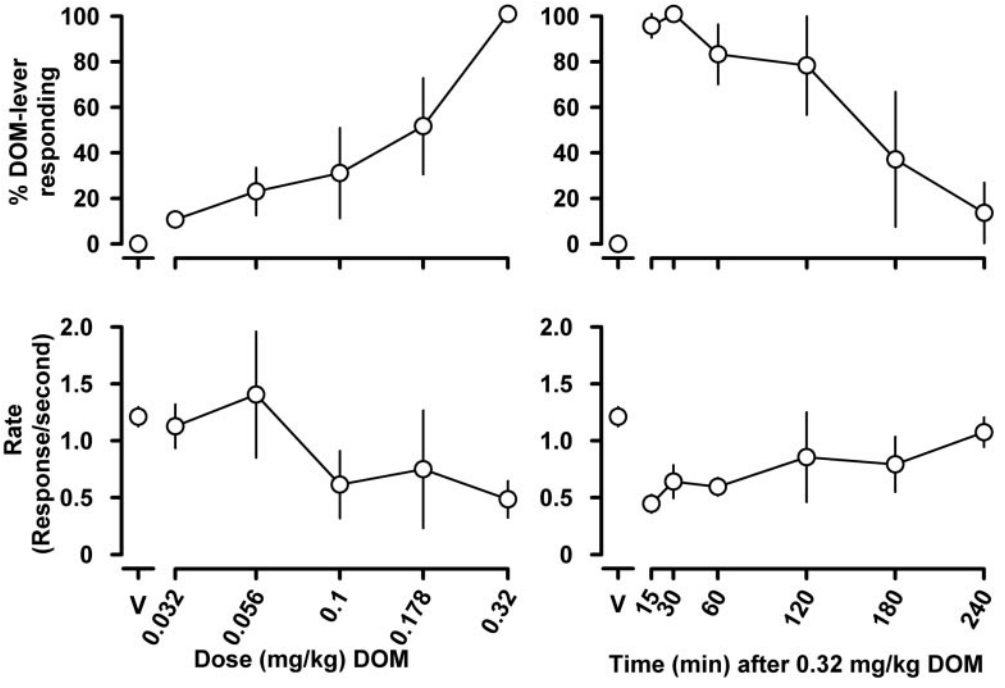

Fig. 1. Discriminative stimulus and rate effects of DOM in rhesus monkeys. Each point represents the average (±S.E.M.) of four monkeys. Ordinates: top panels, average percentage of responses of the DOM-associated lever; bottom panels, average rate of responding in response per second. Abscissae: left panels: dose in milligram per kilogram 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.

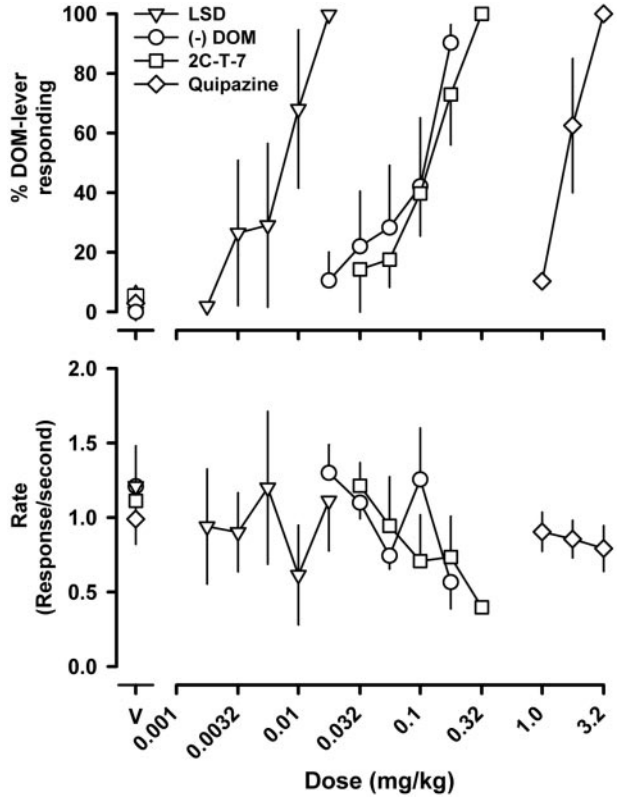

Fig. 2. Discriminative stimulus and rate effects of LSD, (−)DOM, 2C-T-7, and quipazine. See Fig. 1 for other details.

tamine 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 maximal 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, whereas 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.

MDL100907, ketanserin, ritanserin, and MDL100009 each dose-dependently attenuated the discriminative stimulus effects of the training dose (0.32 mg/kg) of DOM (Fig. 3, top), with the largest dose of each decreasing DOM-lever responding to less than 10% (MDL100907 AD_{50} = 0.002 mg/kg [0.001, 0.004]; ketanserin AD_{50} = 0.075 mg/kg [0.029, 0.120]; ritanserin AD_{50} = 0.168 mg/kg [0.042, 0.338]; and MDL100009 AD_{50} = 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.

TABLE 1
Discriminative stimulus and rate effects of drugs in monkeys discriminating between saline and 0.32 mg/kg DOM

	Dose	% Drug-Lever ± S.E.M.	Rate ± S.E.M.
	mg/kg		*response/s*
Compound			
Saline		0 ± 0	1.21 ± 0.09
Amphetamine	0.178	0 ± 0	2.14 ± 0.27
	0.32	5 ± 3	1.82 ± 0.37
	0.56	0 ± 0	1.55 ± 0.16
	1.0	5 ± 3	1.50 ± 0.37
	1.78	0 ± 0	1.78 ± 0.19
Cocaine	0.56	3 ± 1	1.85 ± 0.07
	1.0	4 ± 2	1.46 ± 0.14
	1.78	1 ± 1	1.91 ± 0.24
	3.2	0 ± 0	1.92 ± 0.36
Fenfluramine	1.0	3 ± 3	0.82 ± 0.23
	3.2	1 ± 1	0.53 ± 0.15
	10	18 ± 18	0.45 ± 0.11
Ketamine	1	13 ± 7	0.91 ± 0.32
	1.78	21 ± 10	1.08 ± 0.32
	3.2	38 ± 16	0.57 ± 0.09
	5.6	8 ± 8	0.36 ± 0.15
	10	N.D.	0 ± 0
Methamphetamine	0.32	0 ± 0	1.66 ± 0.07
	0.56	0 ± 0	1.96 ± 0.27
	1.0	0 ± 0	1.34 ± 0.16
Morphine	1.78	1 ± 1	1.24 ± 0.28
	3.2	10 ± 10	1.01 ± 0.30
	5.6	0 ± 0	1.59 ± 0.58
	10	4 ± 4	1.56 ± 0.30
N-0434	0.032	1 ± 1	1.24 ± 0.29
	0.1	4 ± 4	2.07 ± 0.31
	0.178	2 ± 2	2.10 ± 0.35
Phencyclidine	0.1	3 ± 2	0.85 ± 0.12
	0.178	15 ± 14	1.13 ± 0.12
	0.32	45 ± 13	0.41 ± 0.25
Salvinorin A	0.0032	0 ± 0	1.47 ± 0.09
	0.0056	0 ± 0	1.63 ± 0.15
	0.01	0 ± 0	1.71 ± 0.13
	0.0178	1 ± 1	1.94 ± 0.23
	0.032	1 ± 1	1.71 ± 0.29
	0.056	0 ± 0	1.45 ± 0.19
	0.1	9 ± 5	0.71 ± 0.08
U-50488	0.1	1 ± 1	1.58 ± 0.45
	0.178	0 ± 0	1.62 ± 0.33
	0.32	6 ± 3	1.37 ± 0.41
	0.56	2 ± 2	0.55 ± 0.15
	1	0 ± 0	0.45 ± 0.14
Yohombine	0.032	0 ± 0	0.91 ± 0.20
	0.056	1 ± 1	1.21 ± 0.33
	0.1	17 ± 17	1.14 ± 0.37
	0.178	0 ± 0	1.13 ± 0.21
	0.32	0 ± 0	1.13 ± 0.06
	0.56	0 ± 0	1.10 ± 0.30
	1.0	0 ± 0	1.10 ± 0.15
8-OH-DPAT	0.1	0 ± 0	1.35 ± 0.37
	0.178	0 ± 0	1.25 ± 0.50
	0.32	0 ± 0	0.09 ± 0.06

N.D., not determined.

MDL100907 antagonized the discriminative stimulus effects of 3.2 mg/kg DOM within 5 min of its administration and continued to do so in some monkeys for several hours. This antagonism decreased slightly when MDL100907 was administered 2 h or more before DOM and was no longer evident 8 h after administration (Fig. 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

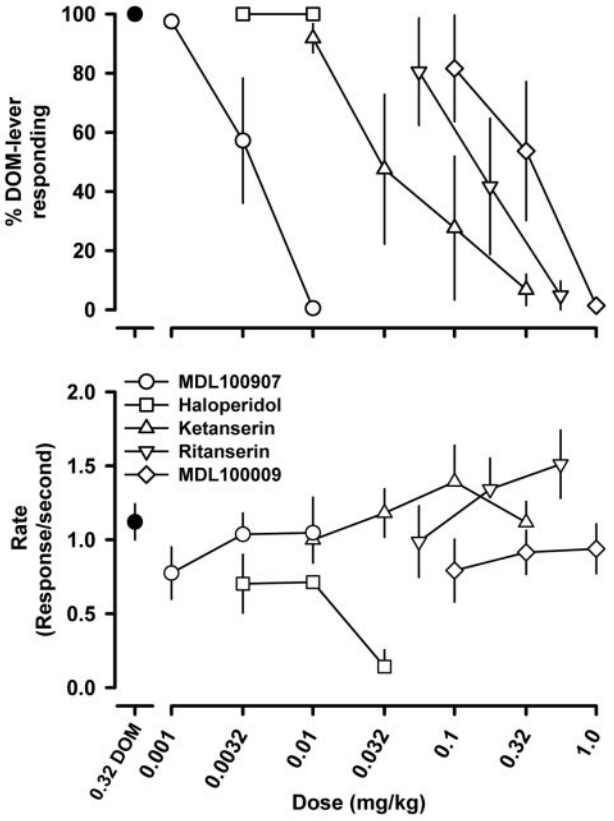

Fig. 3. Antagonism of the discriminative stimulus of 0.32 mg/kg of DOM by MDL 100907, ketanserin, ritanserin, and MDL100009 and lack of antagonism by haloperidol. See Fig. 1 for other details.

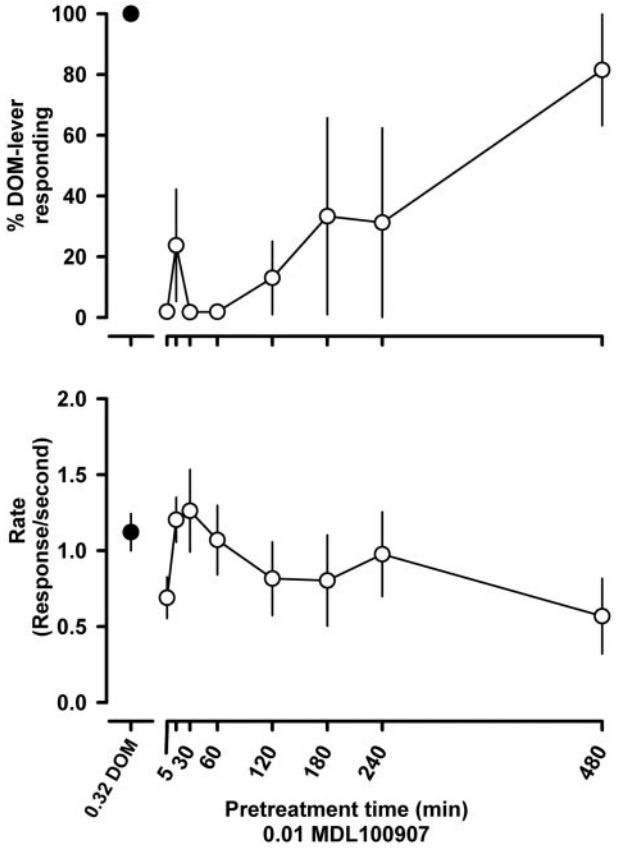

Fig. 4. Time course of antagonism by MDL100908 of 0.32 mg/kg DOM. See Fig. 1 for other details.

less in nonhuman primates and other species. In fact, there is only a single published report (Nielsen, 1985) of nonhuman 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 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 and France, 1996). The discriminative stimulus effects of DOM remained stable throughout the course of these studies (2 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. In humans, DOM is reported to have a very long duration of action (14–20 h) 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 nonhuman 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-HT_2 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 it suggests that 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). In addition, 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 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. Likewise, 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_{1A} receptor agonist 8-OH-DPAT did not occasion DOM-lever responding while dose-dependently decreasing responding. The fact 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 nonselectively disrupt discrimination performance (e.g., Jackson et al., 1992).

MDL100907 is an antagonist at 5-HT receptors with greater than 100-fold selectivity for 5-HT_{2A} receptors (K_i = 0.85 nM) compared with 5-HT_{2C} receptors (K_i = 88 nM) (Kehne et al., 1996). MDL100907 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, compared with those transfected with 5-HT_{2C} receptors, and it potently blocks 5-HT_{2A} receptor agonist-induced head twitches in 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 MDL100907 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 h 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 κ-opioid receptor agonist (Roth et al., 2002) that shares discriminative stimulus effects with prototypic κ-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 κ-agonist activity (Arasteh et al., 1999). In monkeys, salvinorin A and the prototypic κ-opioid receptor agonist U-50488 failed to occasion responding on the DOM-associated lever, up to doses that markedly decreased responding. The fact 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 these hallucinogens vary significantly or that drug discrimination procedures in nonhumans 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 κ-opioid agonists and 5-HT agonists) exert qualitatively different discriminative stimulus effects in nonhumans. These results provide the first direct evidence for a high degree of concordance in the discriminative stimulus effects of prototypic hallucinogens between rodents and nonhuman primates. Given the value of nonhuman 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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