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ORIGINAL INVESTIGATION

Estimating the relative reinforcing strength of (±)-3,4-methylenedioxymethamphetamine (MDMA) and its isomers in rhesus monkeys: comparison to (+)-methamphetamine

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Abstract
Rationale (±)3,4-Methylenedioxymethamphetamine (MDMA) is an analog of methamphetamine (MA) and a drug of abuse. MA, MDMA, and its isomers release monoamine neurotransmitters with varying selectivities and would, therefore, be predicted to vary in their relative strength as reinforcers.
Objectives This study compared self-administration of MA, MDMA, and its isomers using a progressive-ratio schedule in rhesus monkeys.
Methods Rhesus monkeys [n=6, MA and MDMA; n=5, (+)-MDMA and (−)-MDMA] were prepared with chronic i.v. catheters and allowed to self-administer cocaine or saline in daily baseline sessions. When responding was stable, MA (0.006–0.1 mg/kg per injection), MDMA (0.025–0.8 mg/kg injection), (+)-MDMA (0.025–0.8 mg/kg per injection), or (−)-MDMA (0.05–0.8 mg/kg per injection) was made available in test sessions.
Results MA, MDMA, and (+)-MDMA functioned as positive reinforcers in all monkeys with a potency relationship of MA>(+)-MDMA>(±)-MDMA. Two of five monkeys took (−)-MDMA above saline levels. Dose–response relationships were biphasic for MA and (±)-MDMA, and asymptotic for (+)-MDMA. In terms of maximum number of injection per session, a measure of relative reinforcing strength, the order was MA>(+)-MDMA=(±)-MDMA>(−)-MDMA.
Conclusions MDMA and (+)-MDMA were consistent positive reinforcers, but weaker than MA, whereas (−)-MDMA was, at best, a weak reinforcer in some monkeys. The reinforcing strength of MDMA appears to derive primarily from (+)-MDMA. Because MDMA and its isomers have been shown to have relatively higher serotonin to dopamine releasing potency, these data support the hypothesis that increasing 5-HT releasing potency relative to DA is associated with weaker reinforcing effects.

Keywords Drug abuse · Self-administration · Monkey · 3,4-Methylenedioxymethamphetamine · MDMA · Methamphetamine · Reinforcement · Monoamine · Dopamine · Serotonin

Introduction

Evidence is strong that dopaminergic actions are positively associated with reinforcing effects of drugs that act by increasing monoamine neurotransmission in the central nervous system (CNS) (Bergman et al. 1989; Ritz et al. 1987). Evidence is accumulating that enhanced serotonergic activity is negatively associated with reinforcing effects. Compounds that selectively increase serotonin (5-HT) neurotransmission have been found neither to maintain self-administration by animals (Howell and Byrd 1995; Tessel and Woods 1975; Vanover et al. 1992) nor to have abuse liability in humans (Haddad 1999; Zawertailo et al. 1995). Among amphetamine-like drugs that are not as selective for 5-HT releasing activity, Ritz and Kuhar (1989) reported a negative correlation between potency as a reinforcer and binding affinity at the 5-HT transporter (SERT). We have recently reported self-administration results with a series of amphetamine analogs in monkeys that reached similar conclusions (Wee et al. 2005).

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Reinforcing strength among a series of cocaine analogs has also been shown to be negatively related to the SERT relative to dopamine transporter (DAT) potency (Roberts et al. 1999). Taken together, these data suggest that among drugs that increase monoaminergic neurotransmission in the CNS, increasing 5-HT activity may reduce self-administration, indicative of reduced reinforcing strength.

(±)-Methylenedioxymethamphetamine (MDMA) is a ring-substituted analog of methamphetamine (MA). Both MDMA and MA release monoamines in the CNS. Whereas MA is about 30-fold more potent in vitro as a releaser of dopamine (DA) than 5-HT, MDMA is a more potent releaser of 5-HT than of DA, by approximately six- to sevenfold (Rothman et al. 2001). Considering that increased 5-HT potency relative to DA appears to reduce reinforcing strength, MDMA might be predicted to be a relatively weaker reinforcer than MA. Research has demonstrated that MDMA, like MA, can function as a positive reinforcer in monkeys (Beardsley et al. 1986; Fantegrossi et al. 2002; Lamb and Griffiths 1987) and rats (Ratzenboeck et al. 2001; Schenk et al. 2003), although concerns have recently been raised about the relevance to the human situation of MDMA self-administration by rats (De La Garza et al. 2006). Although these studies did not provide estimates of relative reinforcing strength, MDMA sometimes maintained less responding than other drugs. Lile et al. (2005) recently found MDMA to be a weaker reinforcer than cocaine in monkeys responding under a progressive-ratio (PR) schedule of reinforcement.

The purpose of the present study was to use a PR schedule of reinforcement to compare the relative reinforcing strength of MDMA, its (+)-, and (−)-isomers and MA. Because MDMA is a more potent releaser of 5-HT than DA, it was hypothesized that MDMA would be a weaker reinforcer than MA. Additionally, because (−)-MDMA is more selective for 5-HT release than MDMA or (+)-MDMA (Rothman et al. 2001; Setola et al. 2003), we hypothesized that (−)-MDMA would be a weaker reinforcer than MDMA and (+)-MDMA. It is interesting to note that both isomers have been reported to function as positive reinforcers in monkeys responding under a fixed-ratio schedule (Fantegrossi et al. 2002, 2004). Neither isomer has been evaluated under conditions that allow estimates of relative reinforcing strength.

Materials and methods

All animal use procedures were approved by the University of Mississippi Medical Center's Animal Care and Use Committee and were in accordance with National Institutes of Health guidelines.

Animals and apparatus

The subjects were six male rhesus monkeys (*Macaca mulatta*) weighing between 9.7 and 12.0 kg at the beginning of the study. All monkeys had extensive histories of drug self-administration. Most recently, monkeys M1389, AV88, M341, and L500 had participated in a study of self-administration of mixtures of *d*-amphetamine and fenfluramine under the schedule of reinforcement used in the present study (Wee and Woolverton 2006). Monkey M477 had a history of choosing between injections of cocaine and food under a discrete-trials paradigm (unpublished). Monkey R0805 had a history of choosing between injections of cocaine and cocaine + histamine (unpublished). All monkeys were provided with sufficient food (154–238 g/day, Teklad 25% Monkey Diet, Harlan/Teklad, Madison, WI, USA) to maintain stable body weight and had unlimited access to water. Fresh fruit and a vitamin supplement were provided daily and three times a week, respectively. Lighting was cycled to maintain 16 h of light and 8 h of dark, with lights on at 06:00 h.

The monkeys were individually housed in the experimental cubicles (1.0 m^3, PlasLabs, Lansing, MI, USA). Each monkey was fitted with a stainless-steel harness attached by a tether to the rear wall of the cubicle. The front door of the cubicle was made of transparent plastic and the remaining walls were opaque. Two response levers (PRL-001, BRS/LVE, Beltsville, MD, USA) were mounted on the inside of the door. Four jeweled stimulus lights, two red and two white, were mounted above each lever. Drug injections were delivered by a peristaltic infusion pump (Cole-Parmer, Chicago, IL, USA). A Macintosh computer with custom interface and software controlled all events in an experimental session.

Procedure

Monkeys were implanted with a silastic catheter (0.26 cm o.d.×0.076 cm i.d.; Cole–Parmer, Chicago, IL, USA) into the jugular (internal or external) or femoral vein under isoflurane anesthesia. Brachial veins were implanted with a microrenethane catheter (0.2 cm o.d.×0.1 cm i.d.; Braintree Scientific, Braintree, MA, USA) heated and drawn to approximately half size. The proximal end of the catheter was inserted into the vein and terminated in the vena cava near the right atrium. The distal end was threaded subcutaneously to exit the back of the monkey, threaded through the spring arm, out the rear of the cubicle and connected to the peristaltic pump. In the event of catheter failure, surgery was repeated using another vein, after the veterinarian confirmed the health of the monkey.

Experimental sessions began at 11:00 each day and were conducted 7 days per week. Thirty minutes before each

session started, catheters were filled with drugs for the sessions without infusing the drugs into monkeys. At the start of a session, the white lights were illuminated above both levers and pressing the right lever resulted in the delivery of a drug injection for 10 s. During the injection, the white lights were extinguished and the red lights were illuminated. Pressing the left lever was counted but had no other programmed consequence. After the session, catheters were filled with 0.9% saline containing heparin (40 U/ml).

Drugs were made available to monkeys in which responding was maintained under a progressive-ratio (PR) schedule of reinforcement comparable to that described by Wilcox et al. (2000). The PR schedule consisted of 20 trials, with one injection available per trial. In five monkeys, the response requirement started at 100 responses per injection and doubled after every fourth trial. In the sixth monkey (R0805), responding was not well maintained under these conditions so the sequence began at 10 responses/injection and doubled as described. A subject had 30 min to complete a trial (limited hold 30 min: LH 30′). A trial ended with a 10-s drug injection or the expiration of the LH. There was a 30-min timeout (TO 30′) after each trial. If the response requirement was not completed for two consecutive trials (i.e., the LH expired), or the animal self-administered all 20 injections, the session ended.

In baseline sessions, cocaine or saline was available for an injection. The baseline dose of cocaine or saline was initially available under a double-alternation schedule, i.e., two consecutive daily cocaine sessions were followed by two consecutive daily saline sessions. When responding was stable (running mean for each type of baseline session within ±2 injections, and four or fewer injections/session in saline sessions) for at least two consecutive double-alternation sequences (i.e., eight sessions), test sessions were inserted to the daily sequence between two saline and two cocaine sessions. Additionally, to prevent monkeys from learning this session sequence, a randomly determined saline or cocaine baseline session was inserted after every other test session. Thus, the daily sequence of sessions was C, S, T, S, C, T, R, C, S, T, S, C, T, R, where "C", "S", "R", and "T", respectively, represent a cocaine baseline, a saline, a randomly determined cocaine/saline, and a test session. The baseline dose of cocaine was the lowest dose that maintained the maximum injections in an individual monkey, i.e., 0.2 or 0.4 mg/kg per injection. During test sessions, one of various doses of methamphetamine (MA; 0.006–0.1 mg/kg per injection), (±)-methylenedioxymethamphetamine (MDMA; 0.025–0.8 mg/kg per injection), (+)-MDMA (0.025–0.8 mg/kg per injection), or (−)-MDMA (0.05–0.8 mg/kg per injection) were available for monkeys under conditions identical to baseline sessions. All doses were tested at least twice in each monkey, once with a saline session the day before and once with a cocaine session the day before. When the two test sessions of a dose showed high variability (the number of injections exceeded ±3 injections of the mean), the dose was redetermined twice, once after saline session and once after cocaine baseline session. If the redetermined effects were stable, then three sessions of four were at the stable level and the mean of the redetermined doses was used for data analysis. If the redetermined effects were variable like the initially determined effects, all four sessions were used to calculate the mean. MA was tested first and MDMA second in all monkeys, and the isomers were tested afterward in different orders across monkeys. For all drugs, doses were available in an irregular order across monkeys. With occasional exceptions, all doses of one compound were tested before moving on to the next compound. After a test session, a monkey was returned to baseline conditions until responding for cocaine and saline again met stability criteria, or a new stable baseline was established.

Data analysis

The mean number of injections per session was calculated individually from the test sessions as a function of dose (see DePoortere et al. 1993; Rowlett et al. 1996). The range of injections served as a measure of variability in individual subjects. A dose of a drug was considered to function as a reinforcer if the mean number of injections was above levels seen with saline and the ranges did not overlap.

For potency comparisons, ED_{50} values were calculated from log dose–response functions for individual animals in which a drug served as a reinforcer using the ascending limb of the dose–response function and nonlinear regression analysis with mean levels of saline self-administration in baseline sessions and maximum number of injections of the test drug serving as minimum and maximum values, respectively for the analysis (GraphPad Prism 4.0). Mean ED_{50}s were calculated for each drug by averaging the log values of ED_{50}s in all monkeys in which the drug functioned as a reinforcer and taking the antilog of that value. The maximum number of injections, regardless of dose, was used as a measure of reinforcing strength in an individual subject and mean values were calculated for each drug. Statistical significance of between-drug differences for both ED_{50} and maximum injections was analyzed using one-way analysis of variance (ANOVA). A significant ANOVA was followed by Newman–Keuls multiple comparison tests with statistical significance set at the $P=0.05$ level.

Drugs

All drugs were provided by National Institute on Drug Abuse and were dissolved in 0.9% saline. Doses are expressed as the salt forms of the drugs.

Results

The baseline dose of cocaine maintained a mean of 17.3 injections/session (SEM=0.8; Fig. 1), while saline maintained a mean of 2.7 injections/session (SEM=0.2). MA, MDMA, and (+)-MDMA functioned as positive reinforcers in all monkeys. Dose–response functions increased with dose over low to moderate doses and were asymptotic or decreased again at higher doses (Fig. 1). The rank order of potency of drugs was MA (ED_{50}=0.03±0.005 SEM)>(+)-MDMA (ED_{50}=0.11±0.015)>MDMA (ED_{50}=0.2±0.013) [F (2,14)=56.43; P<0.001]. MA was about fourfold more potent than (+)-MDMA and (+)-MDMA was twofold more potent than MDMA. (−)-MDMA failed to maintain self-administration at any dose in three of five monkeys.

The rank order for maximum injections/session (Fig. 2) was MA (13±1 SEM)>MDMA (9±1 SEM)=(+)-MDMA (10±1 SEM)>(−)-MDMA (4.7±0.8 SEM) [F(3,18)=65.3; P<0.001]. (−)-MDMA maintained maximum self-administration of seven injections/session at 0.8 mg/kg per injection (monkey AV88) and nine injections/session at 0.4 mg/kg per injection (monkey L500). Responding was below saline levels at all doses in other monkeys.

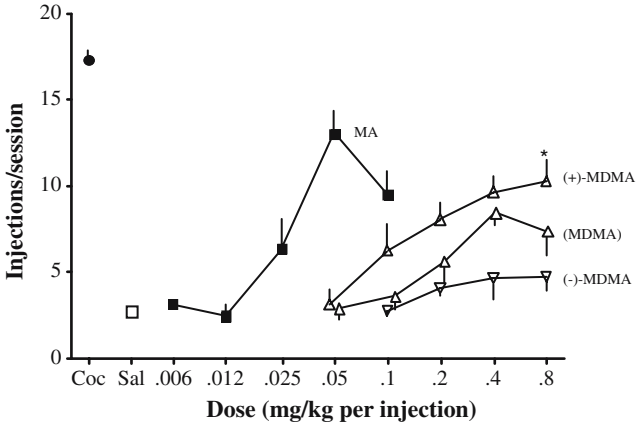

Fig. 1 Dose–response functions for self-administration of MA, MDMA, (+)-MDMA, and (−)-MDMA under a progressive-ratio schedule of reinforcement. *Data points* represent the mean injections/session for six (MA and MDMA) or five monkeys [(+)-MDMA and (−)-MDMA] except at 0.8 mg/kg per injection (+)-MDMA (*asterisk*) where n=2. *Vertical bars* represent the SEM values

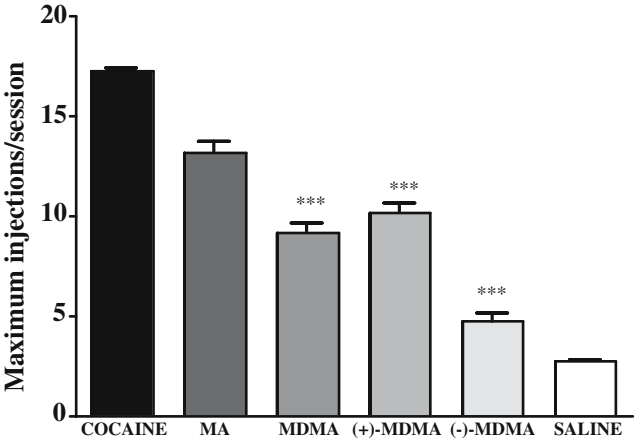

Fig. 2 Average injections of cocaine and saline in baseline sessions and maximum injections of MA, MDMA, (+)-MDMA, and (−)-MDMA under a progressive-ratio schedule of reinforcement. Each *data point* represents the mean maximum injections/session for six (MA and MDMA) or five monkeys (+)-MDMA and (−)-MDMA and *vertical bars* represent the SEM values. ***P<0.001 compared to MA

Discussion

MDMA functioned as a positive reinforcer in rhesus monkeys responding under a PR schedule of reinforcement. This finding is consistent with previous reports from studies with rats (Ratzenboeck et al. 2001; Schenk et al. 2003), rhesus monkeys (Beardsley et al. 1986; Fantegrossi et al. 2002; Fantegrossi 2006; Lile et al. 2005) and baboons (Lamb and Griffiths 1987), and with the well-established abuse liability of MDMA (Strote et al. 2002; Yacoubian 2003). The study by Lile et al. (2005) used a PR schedule similar to the one used in the present study, but with a different progression in response requirement and a shorter TO between injections. The potency of MDMA was comparable to that seen in the present study with responding generally being maintained between 0.1 and 0.56 mg/kg per injection. Responding was maintained by MDMA in the Lile et al. (2005) study at breakpoints between 128 and 444 in three of the four monkeys in that study. In the fourth monkey, breakpoint was over 2,000 responses/injection. Breakpoint is not as clearly defined in the present study because multiple injections were available at each response requirement. What can be said is that MDMA maintained an average of nine injections/session in the present study, the ninth injection having a response requirement of 400 responses/injection. Thus, the maximum response requirements maintained by MDMA were also comparable across studies.

Maximum responding maintained by MDMA was lower than that maintained by MA in the present study and lower than that maintained by cocaine in the Lile et al. (2005) study. Although complete dose–response functions were not determined for cocaine in the present study, the baseline

dose was selected in each monkey to be the dose that maintained maximum responding. Baseline cocaine dose clearly maintained higher responding than MDMA. Previous studies using FR schedules of reinforcement in monkeys have reported less self-administration of MDMA than *d*-amphetamine (Beardsley et al. 1986), cocaine (Lamb and Griffiths 1987), and MA (Fantegrossi et al. 2002). Although rate of self-administration under FR schedules does not always predict reinforcing strength, taken together with the present findings, these studies converge on the conclusion that MDMA is a somewhat weaker positive reinforcer than other prominent drugs of abuse, at least in the psychomotor stimulant class. This may seem somewhat surprising given MDMA's notoriety as a drug of abuse. Indeed, research with human subjects has suggested that MDMA is at least comparable to *d*-amphetamine in its value as a reinforcer and positive subjective effects (Cami et al. 2000; Tancer and Johanson 2003). According to recent statistics (SAMHSA 2004), however, cocaine use by individuals older than 12 in the past month, year or lifetime exceeds MDMA use by approximately threefold, while differences between MA and MDMA are small. Although many factors in addition to reinforcing strength determine actual abuse, it may be that the subjective effects of MDMA related to dysphoria (Cami et al. 2000) are contribute to its diminished reinforcing strength relative to other abused drugs. These authors reported dysphoria-related effects of 125 mg of MDMA as measured by the Addiction Research Center Inventory and the Profile of Mood States subjective effect scales.

Fantegrossi et al. (2002) reported that MDMA and its isomers served as positive reinforcers in rhesus monkeys responding under a FR 10 schedule, and that there were no substantial differences between the drugs in rates of self-administration. The primary novel finding of the present study is that under a PR schedule, MDMA and the (+)-isomer maintained substantially more responding than did (−)-MDMA. Indeed, (−)-MDMA did not function as a reinforcer in the majority of monkeys. Differences between the present findings and those of Fantegrossi et al. (2002, 2004) can likely be attributed to differences in response requirement between the FR 10 schedule they used and the response requirement in the present study that, in all but one monkey, increased from 100. Although MDMA self-administration has been reported to decrease with repeated dose–response determinations over time (Fantegrossi et al. 2004), it seems unlikely that this effect contributed to the present results. Complete dose–response functions were determined only once in the present study. The (+)-isomer was, as would be expected, approximately twice as potent as the racemic mixture as a reinforcer. Based on these observations, it is reasonable to conclude that the reinforcing strength of MDMA is mediated primarily by the (+)-isomer.

Table 1 presents the relative potency, established in other studies, for in vitro monoamine release by MA, MDMA, and its isomers. These comparisons should be considered with the caveat that they were collected in different studies, which could have influenced the results. Nevertheless, it is worth noting the potency relationship for DA release of MA>(+)-MDMA>MDMA>(−)-MDMA is identical to the potency relationship of these compounds as reinforcers in the present study, consistent with the conclusion that DA is involved in the reinforcing effect. Previous studies with both cocaine-like (Roberts et al. 1999) and amphetamine-like (Wee et al. 2005) compounds have also suggested that those with increased 5-HT potency relative to DA potency are weaker reinforcers. The present results are generally consistent with this conclusion as well. However, although maximum responding maintained by the (+)-isomer was slightly higher than that maintained by the racemate, the difference did not achieve statistical significance. That is, the compound with the lower DA/5-HT potency ratio was not clearly a stronger reinforcer. It may be that the DA and 5-HT potency differences between (+)-MDMA and MDMA were too small to influence reinforcing strength. Alternatively, the present PR schedule does not have adequate resolution to distinguish small differences in relative reinforcing strength. In any case, the compound with the lowest DA/5-HT potency ratio, MA, was clearly the strongest reinforcer while the compound with the highest DA/5-HT ratio, (−)-MDMA was the weakest reinforcer.

Although the present results lend support, the conclusion that increased 5-HT actions relative to DA can decrease reinforcing strength, it should be pointed out that Lile et al. (2003) reported self-administration by monkeys of a cocaine analog and DA uptake blocker, HD-60, with at least 80-fold selectivity for SERT relative to the DAT binding. Other compounds tested in monkeys that support

Table 1 In vitro potency as releasers of monoamine neurotransmitters

	EC_{50} (nM)			DA/NE	DA/5-HT
	[^{3}H] DA	[^{3}H] NE	[^{3}H] 5-HT		
(+)-Methamphetamine[a]	24.5±2.1	12.3±0.7	736±45	2.0	0.033
(+)-MDMA[b]	142±4	136±9	74±3	1.04	1.92
(±)-MDMA[a]	376±16	77.4±3.4	56.6±2.1	4.86	6.6
(−)-MDMA[b]	3700±100	560±40	340±20	6.61	10.88

Values are mean±SD for three experiments.
[a] From Rothman et al. 2001
[b] From Setola et al. 2003

the DA/5-HT hypothesis have been primarily monoamine releasers (Ritz and Kuhar 1989; Wee et al. 2005), raising the possibility that there is a difference between monoamine release and reuptake blockade in terms of reinforcing effects. It is interesting to note that HD-60 was not a positive reinforcer in rats in the study of Roberts et al. (1999; called WF-60), raising the additional possibility of a species difference on this dimension. Along these lines, it should be noted that the data in Table 1 were taken from rat brain tissue. Thus, although there is reason to believe that the relative mixture of DA and 5-HT actions can influence reinforcing strength, some significant ambiguities still exist.

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References

Beardsley P, Balster R, Harris L (1986) Self-administration of methylenedioxymethamphetamine (MDMA) by rhesus monkeys. Drug Alcohol Depend 18:149–157

Bergman J, Madras BK, Johnson SE, Spealman RD (1989) Effects of cocaine and related drugs in nonhuman primates. III. Self-administration by squirrel monkeys. J Pharmacol Exp Ther 251:150–155

Cami J, Farre M, Mas M, Roset PN, Poudevida SP, Mas A, San L, de la Torre R (2000) Human pharmacology of 3,4-methylenedioxymethamphetamine ("Ecstasy"): psychomotor performance and subjective effects. J Clin Psychopharmacol 20:455–466

De La Garza R, Fabrizio KR, Gupta A (2006) relevance of rodent models of intravenous MDMA self-administration to human MDMA consumption patterns. Psychopharmacology (in press). DOI 10.1007/s00213-005-0255-5

Depoortere RY, Li DH, Lane JD, Emmett-Oglesby MW (1993) Parameters of self-administration of cocaine in rats under a progressive-ratio schedule. Pharmacol Biochem Behav 45:539–548

Fantegrossi WE (2006) Reinforcing effects of methylenedioxy amphetamine congeners in rhesus monkeys: are intravenous self-administration experiments relevant to MDMA neurotoxicity? Psychopharmacology (in press). DOI 10.1007/s00213-006-0320-8

Fantegrossi WE, Ulrich T, Rick KC, Woods JH, Winger G (2002) 3,4-Methylenedioxymethamphetamine (MDMA "ecstasy") and its stereoisomers as reinforcers in rhesus monkeys: serotonergic involvement. Psychopharmacology 161:356–364

Fantegrossi WE, Woolverton WL, Kilbourn M, Sherman P, Yuan J, Hatzidimitriou G, Ricaurte G, Woods JH, Winger G (2004) Behavioral and neurochemical consequences of long-term intravenous self-administration of MDMA and its enantiomers by rhesus monkeys. Neuropsychopharmacology 29:1270–1281

Haddad P (1999) Do antidepressants have any potential to cause addiction? J Psychopharmacol 13:300–307

Howell L, Byrd LD (1995) Serotonergic modulation of the behavioral effects of cocaine in the squirrel monkey. J Pharmacol Exp Ther 275:1551–1559

Lamb RJ, Griffiths RR (1987) Self-injection of d-1-3,4-methylenedioxymethomphetamine (MDMA) in the baboon. Psychopharmacology 91:268–272

Lile JA, Wang Z, Woolverton WL, France JE, Gregg TC, Davies HML, Nader MA (2003) The reinforcing efficacy of psychostimulants in rhesus monkeys: the role of pharmacokinetics and pharmacodynamics. J Pharmacol Exp Ther 307:356–366

Lile JA, Ross JT, Nader MA (2005) A comparison of the reinforcing efficacy of 3,4-methylenedioxyamphetamine (MDMA, "ecstasy") with cocaine in rhesus monkeys. Drug Alcohol Depend 78:135–140

Ratzenboeck E, Saria A, Kriechbaum N, Zernig G (2001) Reinforcing effects of MDMA ("ecstasy") in drug-naive and cocaine-trained rats. Pharmacology 62:138–144

Ritz MC, Kuhar MJ (1989) Relationship between self-administration of amphetamine and monoamine receptors in brain: comparison with cocaine. J Pharmacol Exp Ther 248:1010–1017

Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ (1987) Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237:1219–1223

Roberts DC, Phelan R, Hodges LM, Hodges MM, Bennett B, Childers S, Davies H (1999) Self-administration of cocaine analogs by rats. Psychopharmacology 144:389–397

Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, Partilla JS (2001) Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. Synapse 39:32–41

Rowlett JK, Massey BW, Kleven MS, Woolverton WL (1996) Parametric analysis of cocaine self-administration under a progressive-ratio schedule in rhesus monkeys. Psychopharmacology 125:361–370

Schenk S, Gittings D, Johnstone M, Daniela E (2003) Development, maintenance and temporal pattern of self-administration maintained by ecstasy (MDMA) in rats. Psychopharmacology 169:21–27

Setola V, Hufeisen SJ, Grande-Allen KJ, Vesely I, Glennon RA, Blough B, Rothman RB, Roth BL (2003) 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro. Mol Pharmacol 63:1223–1229

Strote J, Lee JE, Weschler H (2002) Increasing MDMA use among college students: results of a national survey. J Adolesc Health 30:64–72

Substance Abuse and Mental Health Services Administration (2004) 2004 National Survey on Drug Use and Health. DHHS, Rockville, MD

Tancer M, Johanson CE (2003) Reinforcing, subjective and physiological effects of MDMA in humans. Drug Alcohol Depend 72:33–44

Tessel RE, Woods JH (1975) Fenfluramine and N-ethyl amphetamine: comparison of the reinforcing and rate-decreasing actions in the rhesus monkey. Psychopharmacologia 43:239–244

Vanover KE, Nader MA, Woolverton WL (1992) Evaluation of the discriminative stimulus and reinforcing effects of sertraline in rhesus monkeys. Pharmacol Biochem Behav 41:789–793

Wee S, Woolverton WL (2006) Self-administration of mixtures of fenfluramine and amphetamine by rhesus monkeys. Pharmacol Biochem Behav 84:337–343

Wee S, Anderson KG, Baumann MH, Rothman RB, Blough BE, Woolverton WL (2005) Relationship between the serotonergic activity and the reinforcing effects of a series of amphetamine analogs. J Pharmacol Exp Ther 313:848–854

Wilcox KM, Rowlett JK, Paul IA, Ordway GA, Woolverton WL (2000) On the relationship between the dopamine transporter and the reinforcing effects of local anesthetics in rhesus monkeys: practical and theoretical concerns. Psychopharmacology 153:139–147

Yacoubian GS Jr (2003) Tracking ecstasy trends in the United States with data from three national drug surveillance systems. J Drug Educ 33:245–258

Zawertailo LA, Busto U, Kaplan HL, Sellers EM (1995) Comparative abuse liability of sertraline, alprazolam and dextroamphetamine in humans. J Clin Psychopharmacol 15:117–124