Transient reinforcing effects of phenylisopropylamine and indolealkylamine hallucinogens in rhesus monkeys

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Relatively few studies have assessed the reinforcing effects of hallucinogenic compounds, and no such studies have attempted to engender contingent responding for these compounds in animals with behavioral histories that include experience with serotonergically mediated reinforcing effects. The objectives of the present study were to investigate the capacity of several hallucinogenic compounds to maintain self-administration behavior in rhesus monkeys with a previous history of 3,4-methylenedioxymethamphetamine (MDMA) self-administration, and to compare these effects across a range of doses of drugs from two structural classes (indolealkylamines and phenylisopropylamines). The results indicate that no compound generated reliable responding and that no subject ever self-administered 4-iodo-2,5-dimethoxyphenylisopropylamine (DOI) at rates above those engendered by contingent saline. However, 3 out of 4 subjects did respond at rates between 0.75 and 3.0 responses/s in one or more sessions where *N*,*N*-dimethyltryptamine (DMT), mescaline or psilocybin were available. During some of these sessions in which self-administration was maintained, animals earned a majority of all available infusions and appeared intoxicated by the end of the session. This pattern of transient self-administration may indicate that these compounds have weak reinforcing effects, or mixed reinforcing and aversive effects.
***Behavioural Pharmacology* 15:149–157**

Behavioural Pharmacology 2004, **15**:149–157

Keywords: self-administration, indolealkylamines, phenylisopropylamines, hallucinogens, rhesus monkey

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Sponsorship: These studies were supported by USPHS Grants DA09161 and DA05923.

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Received 9 May 2003 **Accepted as revised** 23 January 2004

Introduction

Central serotonin (5-HT) systems have not traditionally been associated with the reinforcing effects of drugs. However, in recent years, a sizeable body of literature describing complex serotonergic involvement in such reinforcing effects has been gradually developing. For instance, decreased 5-HT levels, produced via depletion or lesion, have been associated with increased dopamine (DA) activity in the ventral tegmental area and the nucleus accumbens, two brain areas critically implicated in the reinforcing effects of drugs (White *et al.*, 1995; Morgan *et al.*, 1997). Destruction of 5-HT neurons with 5,7-dihydroxytryptamine (5,7-DHT) likewise appears to increase self-administration of D-amphetamine in rats (Lyness *et al.*, 1980). Additionally, the 5-HT_2 receptor agonists 4-iodo-2,5-dimethoxyphenylisopropylamine (DOI) and 5-methoxydimethyltryptamine (5-OMe DMT) may potentiate DA release induced by the subsequent administration of 3,4-methylenedioxymethamphetamine (MDMA) in rats (Gudelsky *et al.*, 1994). In keeping with serotonergic mediation, pretreatment with the 5-HT_{2A} receptor antagonist M100907 (formerly MDL 100907), or the non-selective 5-HT_2 antagonist amperozide, has been shown to greatly attenuate this latter effect (Schmidt *et al.*, 1994).

We have previously reported on intravenous self-administration of MDMA and its enantiomers in rhesus monkeys, and shown that responding for this compound is almost completely abolished by a dose of M100907 that does not alter responding for contingent injections of intravenous cocaine (Fantegrossi *et al.*, 2002). That R(–)-MDMA functioned as a reinforcer at all was surprising, given that this compound has no measurable effects on DA in rat striatal synaptosomes (Steele *et al.*, 1987) and only minor effects on striatal DA in microdialysis experiments (Hiramatsu and Cho, 1990) in rats. Correspondingly, *N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB), the α-ethyl homologue of MDMA that fully substitutes for MDMA in drug discrimination studies (Oberlender and Nichols, 1990), has been shown to produce conditioned place preference in rats, despite having no effect on striatal DA levels as measured by *in vivo* microdialysis (Marona-Lewicka *et al.*, 1996). These findings strongly suggest that central 5-HT systems may play a role in the reinforcing effects of some drugs.

Notwithstanding the growing indication of serotonergic involvement in reinforcing effects of self-administered drugs, conventional serotonergic hallucinogens have long stood out as a class of drugs that is abused by humans but, nonetheless, fails to engender intravenous

0955-8810 © 2004 Lippincott Williams & Wilkins DOI: 10.1097/01.fbp.0000126062.12518.5c

self-administration in laboratory animals (Poling and Bryceland, 1979). In one study, dimethyltryptamine, a classical 5-HT hallucinogen of the indolealkylamine type, was reported to maintain smoking behavior in isolated and sensory-deprived rhesus monkeys (Siegel and Jarvik, 1980). Despite this single report, accounts of reinforcing effects of the classical hallucinogens with indolealkylamine-, phenylisopropylamine- or ergoline-like structures are uncommon in the experimental literature. Hallucinogenic compounds from all three of these structural classes act as agonists at several post-synaptic 5-HT receptor subtypes, with varying degrees of selectivity, but only their affinity at 5-HT_{2A} receptors is highly correlated with their potency to induce hallucinations in humans (Sadzot *et al.*, 1989).

Explanations for the difficulty in engendering contingent responding for hallucinogens and other serotonergic compounds in laboratory animals may well involve several complex issues, one of which may be the unique self-administration history of the individual subjects. The effects of individual drug-exposure history on initiation of subsequent self-injection and propensity to self-administer specific compounds has been reviewed (Young *et al.*, 1981), and although not previously demonstrated for the hallucinogens, lines of evidence from other pharmacological classes may be relevant. Specifically, Young and Woods (1981) have shown that phencyclidine (PCP), dextrorphan and dexoxadrol maintain behavior in rhesus monkeys with a history of ketamine self-administration but not in animals with a history of codeine self-administration. Also, Beardsley *et al.* (1990) determined that the *N*-methyl-D-aspartate (NMDA) receptor antagonist MK-801 maintains behavior in rhesus monkeys with a history of PCP self-injection, but not in monkeys with a history of cocaine self-administration. A similar dependence on reinforcement history has been established for the self-administration of benzodiazepines (Bergman and Johanson, 1985) and psychostimulants (Schlichting *et al.*, 1970; Nader, 1998).

In view of the importance of behavioral history to the reinforcing effects of drugs, it seems plausible that a behavioral history that includes experience with the reinforcing effects of serotonergic drugs might predispose an organism to self-administer other serotonergic drugs, including hallucinogen-like compounds that otherwise do not maintain behavior. Studies of the reinforcing effects of these compounds in monkeys with a history of prior intravenous self-administration of MDMA, which has primarily (although not exclusively) serotonergic actions, might be useful to assess this possibility. Although not typically classified as an hallucinogenic compound, MDMA is a ring-substituted amphetamine derivative that has structural features common to amphetamine-like psychostimulants, as well as phenylisopropylamine hallucinogens (such as mescaline). The complex neuropharmacological profile of MDMA includes carrier-mediated stimulation of 5-HT release (Nichols *et al.*, 1982; Rudnick and Wall, 1992), blockade of 5-HT reuptake (Nichols, 1986), and direct agonist effects at 5-HT_2 receptors (Teitler *et al.*, 1990). This latter property has been proposed as a major mechanism in the mediation of hallucinogenic effects (Glennon *et al.*, 1984; Sadzot *et al.*, 1989; Aghajanian and Marek, 1999), and seems to be critical for the reinforcing effects of MDMA in rhesus monkeys (Fantegrossi *et al.*, 2002). Furthermore, rats trained to discriminate R(−)-MDMA have fully generalized to cues produced by the classical hallucinogens lysergic acid diethylamide (LSD) (Baker *et al.*, 1995) and mescaline (Baker and Taylor, 1997; but see also Glennon *et al.*, 1982; Oberlender and Nichols, 1988). In our own work, therefore, previous MDMA self-administration may have provided us with a cohort of monkeys that might be uniquely sensitive to the reinforcing effects of other serotonergic drugs. To assess this possibility, we substituted a range of doses of the two indolealkylamine hallucinogens *N*,*N*-dimethyltryptamine (DMT) and psilocybin, as well as the two phenylisopropylamine hallucinogens DOI and mescaline for cocaine in four MDMA-experienced rhesus monkeys.

Methods

Subjects

Four adult rhesus monkeys (three male, one female), with extensive self-administration histories, served as subjects in these studies. All animals weighed between 6.5 and 12 kg and had participated previously in studies with opioids and psychostimulants, as well as with racemic MDMA and its stereoisomers. Animals were individually housed in 83.3 × 76.2 × 91.4 cm-deep stainless-steel cages. A side-mounted panel was present in each cage, equipped with a row of three stimulus lamps (red–green–red) across the top, and two response levers at the bottom (one mounted under each red light). During these studies, each animal wore a Teflon mesh jacket (Lomir, Québec, Canada) connected to a flexible stainless-steel spring arm attached to the rear of the cage. Animals were fed between 10 and 12 Purina monkey chows twice per day, and water was freely available. Daily fresh fruit and other treats supplemented this diet. In accordance with IACUC (Institutional Care and Use Animal Committee) requirements, environmental enrichment toys were also provided on a regular rotating basis.

The surgical preparation of all subjects and the operant schedules used to engender contingent responding for MDMA have been described previously (Fantegrossi *et al.*, 2002). Briefly, subjects were prepared with indwelling intravenous catheters in an internal or external jugular, femoral, or brachial vein under ketamine (10 mg/kg, i.m.) and xylazine (2 mg/kg i.m.) anesthesia. Catheters were run subcutaneously from the implant site to an exit site in

the middle of the back. An external piece of catheter tubing was connected to the indwelling catheter, fed through the steel spring arm and passed to the outside rear of the cage, then connected to drug supplies and additional infusion lines that passed through the rollers of the infusion pump. The infusion pump was calibrated to deliver 1 ml of drug solution over 5 s.

Procedure

Four-component test sessions (130 min) occurred twice daily (at 10.00 and 16.00 hours). In these sessions, monkeys responded under an FR-30, time-out (TO) 45 s schedule of reinforcement for each of four discrete doses of either i.v. cocaine or a substitution drug. This schedule allows for rapid dose–effect curve determinations in rhesus monkeys and was previously used to engender responding for racemic MDMA and its enantiomers (Fantegrossi *et al.*, 2002). Dose components of the session were separated by 10-min time-out periods, during which all stimulus lights were turned off and responses had no programmed consequences. The onset of each dose component was signaled by the illumination of a red stimulus light. In the presence of this light, the thirtieth response on the lever beneath it (FR-30) resulted in operation of the infusion pump. During the infusion, the red stimulus light was extinguished and the central green light was illuminated. Infusion was followed by a 45-second inter-injection time-out period (TO 45 s), during which all lights were turned off and responses had no programmed consequences. Each dose component of this multiple schedule was in effect for a maximum of 20 drug deliveries, or until 25 min had elapsed.

The duration of infusion pump operation differed in the different dose components. The pumps were calibrated to deliver 1 ml of drug solution over a 5-second interval; thus, a higher dose per infusion could be provided by lengthening the infusion interval and, thereby, administering a greater volume of solution. Throughout these experiments the pump durations were 0.5, 1.7, 5.0 and 16.7 s. These durations corresponded to doses of 0.001, 0.003, 0.01 and 0.03 mg/kg per injection when drug reservoir supply bags were filled with a concentration of 0.01 mg/kg per ml. Supply bags were prepared on an individual basis, dependent on the animal's weight. Two higher doses were tested by filling supply bags with a concentration of 0.1 mg/kg per ml (again made on an individual basis, dependent on the animal's weight). Under these latter conditions, the pump durations remained the same but corresponded to doses of 0.01, 0.03, 0.1 and 0.3 mg/kg per injection. The overlapping doses of 0.01 and 0.03 were thus delivered at two different infusion durations; previously, such differences in infusion rate did not affect self-administration (Fantegrossi *et al.*, 2002). Four different orders of pump durations were used in cocaine and saline sessions: an ascending order, a descending order and two mixed orders. The order was selected randomly before each cocaine or saline session; however, all results presented in this report are based upon data obtained in morning sessions under the ascending-order schedule. MDMA and hallucinogen substitution experiments were only conducted under the ascending dose order schedule, and substitutions were always made in morning sessions, no more often than every fourth session. Saline was substituted for the baseline drug (cocaine) approximately every third session. During saline substitution sessions, saline was available during all four components. If responding during any component was > 0.5 response/second, saline was made available in subsequent sessions until this criterion was met. Hallucinogen substitutions began less than 7 days after re-determining the dose–effect function for MDMA self-administration, and the two dose ranges for each drug were tested on three separate occasions.

Drugs

Cocaine hydrochloride, MDMA, DMT and mescaline were supplied by the National Institute on Drug Abuse (Research Technology Branch, Research Triangle Park, North Carolina, USA) S,R(+/−)-DOI was purchased from Sigma Biochemicals (St. Louis, Missouri, USA). Psilocybin was obtained from Sandoz Inc., Pharmaceutical Department (Hanover, New Jersey, USA).

Data analysis

Mean response rates for each dose of self-administered drug were compared by one-way ANOVA and Tukey's HSD *post-hoc* tests, using commercially available statistical software. Single-session data were not analyzed statistically.

Results

Baseline self-administration

Cocaine and MDMA generated 'inverted U'-shaped dose–response curves in all four monkeys in the present experiments: low and high doses of these drugs engendered low rates of responding, while intermediate doses maintained high rates of self-administration behavior. There were marked individual differences in the maximum rate of response engendered by cocaine and MDMA across subjects; however, all monkeys did respond for at least two doses of these compounds at rates significantly higher than those engendered by contingent saline (Table 1). Responding for contingent saline occurred at low rates (< 0.1 response/s) for all animals tested, and no animal ever earned more than 11 saline injections in any dose component. Neither response rates for cocaine nor response rates for MDMA were predictive of subsequent hallucinogen self-administration in any animal.

Indolealkylamines

Mean rates of responding for contingent psilocybin or DMT (aggregated across all monkeys) were < 0.35

Table 1 Response rates for each animal under saline, cocaine and (±)-3,4-methylenedioxymethamphetamine (MDMA) control conditions, expressed as mean ± SEM (three observations per dose)

Monkey	Drug	Saline	0.001	0.003	0.01	0.03	0.1	0.3
92X2643	Cocaine		3.25 ± 0.12*	3.54 ± 0.11*	3.34 ± 0.50*	2.58 ± 0.51*		
	MDMA		2.17 ± 0.74*	2.90 ± 0.21*	3.20 ± 0.15*	2.72 ± 0.51*	2.48 ± 0.37*	0.95 ± 0.26*
	Saline	0.05 ± 0.04						
98X3152	Cocaine		0.65 ± 0.16*	0.84 ± 0.17*	1.31 ± 0.19*	1.43 ± 0.25*		
	MDMA		0.39 ± 0.18*	0.67 ± 0.11*	0.85 ± 0.11*	0.26 ± 0.02		
	Saline	0.08 ± 0.05						
96X4394	Cocaine		1.42 ± 0.28*	2.25 ± 0.06*	2.29 ± 0.28*	2.12 ± 0.26*		
	MDMA				1.81 ± 0.61*	1.9 ± 0.29*	2.24 ± 0.41*	1.55 ± 0.47*
	Saline	0.02 ± 0.11						
94X0352	Cocaine		0.40 ± 0.28	1.08 ± 0.51*	2.32 ± 0.22*	2.59 ± 0.15*		
	MDMA				0.55 ± 0.52	0.49 ± 0.44	1.19 ± 0.35*	0.97 ± 0.21*
	Saline	0.05 ± 0.03						

All doses are expressed in mg/kg per injection. Asterisks indicate significant differences from saline rates ($P < 0.05$) by Tukey's HSD test.

response/s for all doses tested, and an average of less than 8 of 20 available infusions were earned in each dose component (Fig. 1, upper and lower left). No dose of either indolealkylamine compound engendered significantly higher mean response rates than did contingent saline. However, a single subject (monkey 96X4394) did respond at high rates during the first three substitutions for each of the indolealkylamines (Fig. 2). Upon the first exposure to a dose of 0.003 mg/kg per injection DMT, subject 96X4394 responded at a rate of approximately 3.0 responses/s, and earned all 20 available infusions during that component. During the next two DMT sessions, this subject responded for this dose of drug at rates of approximately 0.75 response/s, earning a majority of the 20 available infusions. Similarly, 0.0003–0.01 mg/kg per injection of psilocybin maintained rates between 1.0 and 2.0 responses/s in this subject, and a majority of the 20 available injections were earned in each dose component. Following sessions in which drug intake was high, monkey 96X4394 exhibited several signs of intoxication, including stereotyped visual scanning around the room, head twitches, bizarre body postures, hyperactivity, and 'fly catching' (fixating on an empty point in space and attempting to quickly grasp it). With the exception of hyperactivity, these behaviors were never observed after high intakes of cocaine or MDMA in this animal. Interestingly, the reinforcing effects of these particular doses of DMT and psilocybin proved to be transitory. In both instances, further evaluations resulted in a marked attenuation of self-administration behavior in subject 96X4394, even at doses that previously appeared to have significant reinforcing effects in this animal.

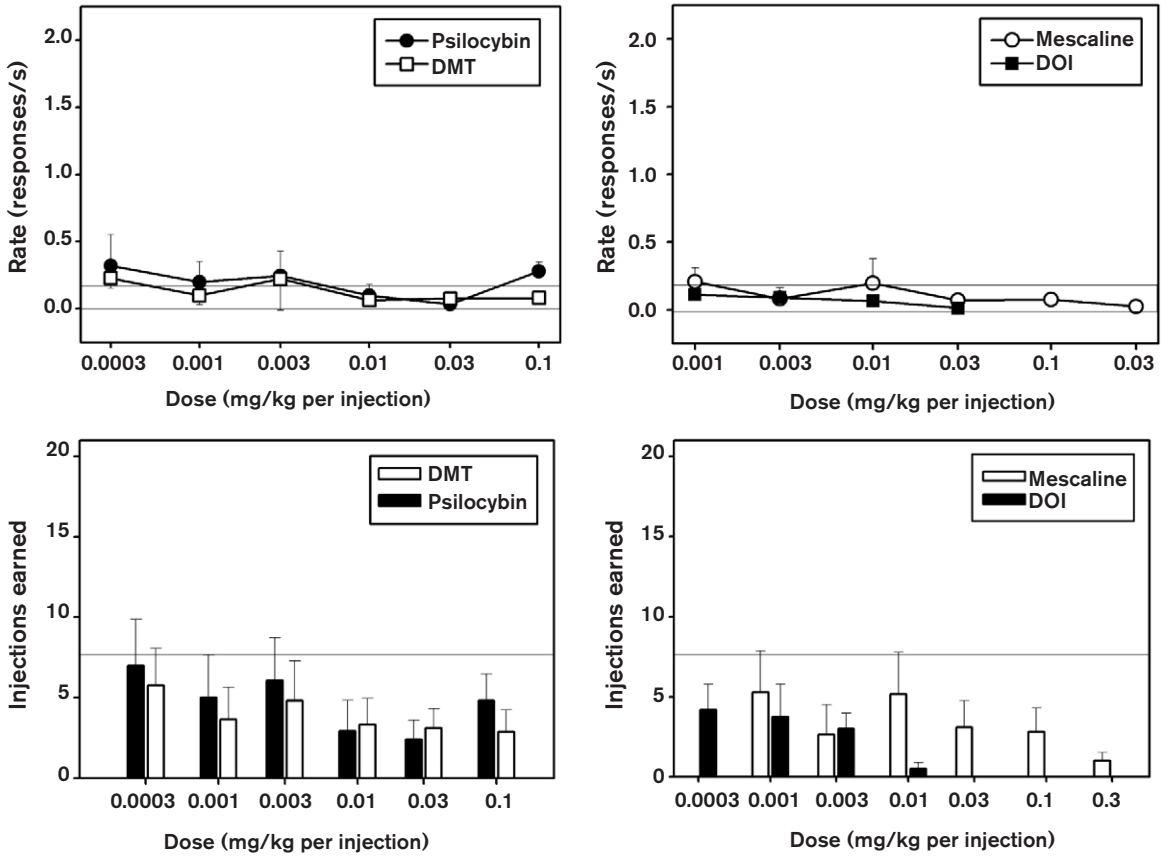
Phenylisopropylamines

As with the indolealkylamines, mean rates of responding for all doses of mescaline or DOI (aggregated across monkeys) were low (< 0.25 response/s), and an average of fewer than 6 of 20 available infusions were earned in each dose component (Fig. 1, upper and lower right). No dose of either phenylisopropylamine compound engendered significantly higher mean response rates than did contingent saline. However, mescaline transiently maintained significant self-administration behavior in subjects 96X4394 (Fig. 2), 92X2643 and 98X3152 (Fig. 3). In the case of subject 96X4394, response rates of approximately 1.0 response/s were engendered by the 0.003 mg/kg per injection dose of mescaline, and all but two available infusions at this dose were earned during the first two substitutions of this compound. Subject 92X2643 had very low rates during the first two exposures to mescaline but, during the third substitution session, responded at a rate of approximately 2.0 responses/s for a dose of 0.01 mg/kg per injection and earned all available infusions of that dose. For subject 98X3152, rates of approximately 1.0 response/s were engendered by doses of 0.001 and 0.003 mg/kg per injection of mescaline during the second of three test sessions, and 19 of 20 available infusions were earned in each component. Behavioral signs of intoxication similar to those previously described following indolealkylamine self-administration were observed in these subjects following sessions in which intakes were high. As was the case with DMT and psilocybin, the apparent reinforcing effects of mescaline did not persist in any subject. Interestingly, DOI failed to maintain i.v. self-administration at any time in any animal.

Discussion

In the present experiments, several monkeys periodically responded at high rates and earned a majority of all available infusions of mescaline, psilocybin and DMT, with no discernible pattern or regularity. Interestingly, DOI was not self-administered by any animal, although subjects had an opportunity to earn up to 0.88 mg/kg of the compound. This dosage of DOI is within the range previously shown to alter repeated acquisition and performance of response sequences in rhesus monkeys (Winsauer and Moerschbaecher, 2000). Thus, it seems unlikely that the lack of self-administration of this compound could simply be due to insufficient dose availability. Importantly, changes across sessions of self-administration for mescaline, psilocybin and DMT did not conform to the typical extinction pattern, in which high response rates are observed initially and gradually

Fig. 1



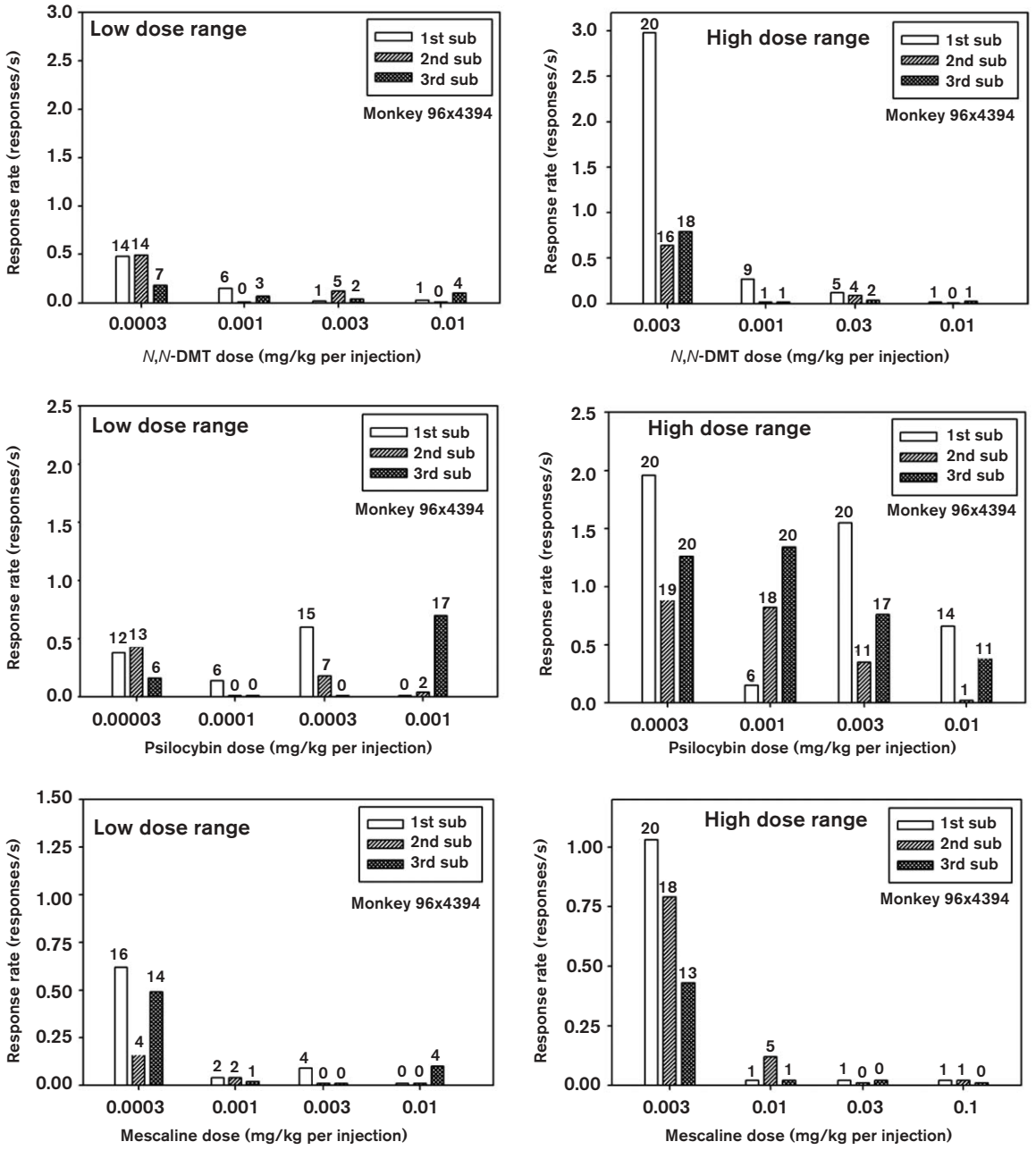
Upper panels: Aggregated response rates for two indolealkylamines (left) and two phenylisopropylamines (right) in rhesus monkeys. Each point represents the mean ± SEM ($n = 4$ for all drugs). Horizontal axes: dose of self-administered drug (mg/kg per injection). Vertical axes: response rate (responses/s). Defined regions represent the range of response rates engendered by contingent saline. Lower panels: Aggregated injections earned for two indolealkylamines (left) and two phenylisopropylamines (right) in rhesus monkeys. Each point represents the mean ± SEM ($n = 4$ for all drugs). Horizontal axes: as above. Defined regions represent the range of earned injections of contingent saline. Vertical axes: number of injections earned (maximum = 20 per dose component).

diminish over continued exposure to a non-reinforcing stimulus. Further, during acute sessions in which significant levels of self-administration occurred, rates of hallucinogen-maintained responding (1.0–3.0 response/s) were far greater than those engendered in sessions in which contingent saline was available (< 0.5 response/s), suggesting that these intermittent sessions of hallucinogen self-administration represent something other than conventional extinction.

The inability of indolealkylamines and phenylisopropylamines to maintain i.v. self-administration behavior is consistent with the results of previous experiments (Deneau *et al.*, 1969; Yanagita, 1986). Apparent negative reinforcing effects of hallucinogenic drugs have been reported previously, and it may be that indolealkylamines and phenylisopropylamines are aversive to laboratory animals. For example, non-contingent administration of LSD or DMT has been shown to increase the frequency of fear grimaces in rhesus monkeys (Siegel *et al.*, 1974), suggestive of aversive drug effects (e.g. Berridge, 2000). Similarly, Hoffmeister and Wuttke (1976) have shown that drug-naïve rhesus monkeys will work to terminate a stimulus associated with infusions of LSD or DOM.

Alternatively, the reinforcing effects of drugs have been shown previously to be influenced by the schedules that govern their contingent delivery (Kelleher and Morse, 1968; Spealman and Goldberg, 1978), and it seems reasonable to assume that the reinforcing effects of some drugs may be appreciated only under particular contingencies. Drugs with 'high reinforcing efficacy' would be expected to maintain behavior across a wide range of operant schedules and behavioral preparations, and this appears to be the case for drugs such as cocaine, amphetamine or heroin (Arnold and Roberts, 1997; Stafford *et al.*, 1998). However, drugs with 'low reinforcing efficacy' might be expected to maintain behavior only

Fig. 2

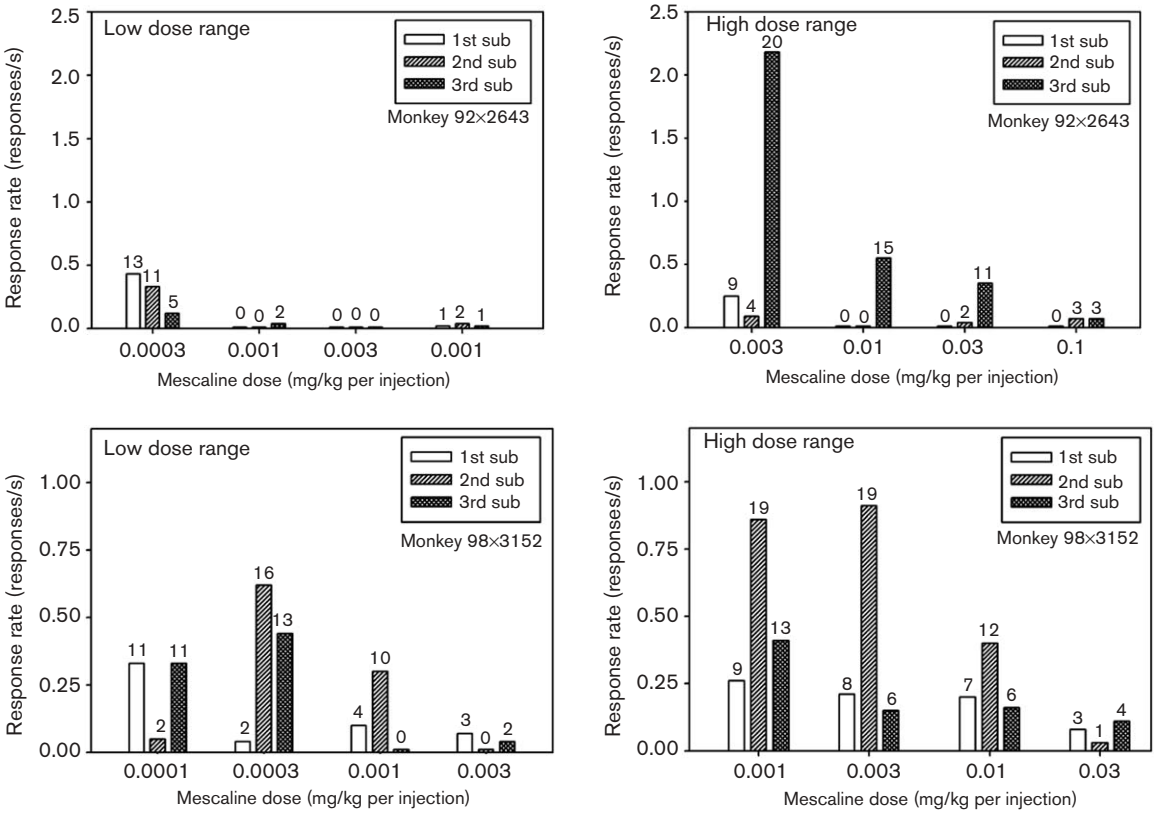


Transient reinforcing effects of dimethyltryptamine (DMT) (top), psilocybin (middle) and mescaline (bottom) in monkey 96X4394 for low dose range substitutions (left panels) and high dose range substitutions (right panels). Each bar represents the absolute response rate for a single dose within a single substitution session; numerals above each bar indicate the number of infusions earned (maximum = 20) for that dose component. Horizontal axes: dose of self-administered drug (mg/kg per injection); vertical axes: response rate (responses/s).

under a limited range of operant schedules or behavioral preparations or, as was observed in the present experiments, perhaps only transiently under some schedule contingencies.

Previous instances of transient reinforcing effects in monkey self-administration experiments have been observed for certain steroids (Broadbear *et al.*, 1999), neurosteroids (unpublished observations) and the CRH-R1 antagonist antalarmin (Broadbear *et al.*, 2002). However, the existing conceptual categorization describing the reinforcing effects of drugs may be inadequate for interpreting these results. While some drugs have previously been shown to possess reinforcing properties

Fig. 3



Transient reinforcing effects of mescaline in monkeys 92X2643 (top) and 98X3152 (bottom). Details are as described in Fig. 2.

only in certain situations – such as under specific schedule contingencies, or following particular behavioral histories (Woods, 1978) – compounds that inconsistently maintain behavior in the same animals studied under unchanging schedule contingencies and access conditions have not been described previously. Further investigations into the 'transient' reinforcing effects of the hallucinogens could help in understanding the variables that control their self-administration by humans and, from a theoretical standpoint, could improve our understanding of the nature of drugs as reinforcers.

As alluded to in the Introduction, it has been claimed that 'animal models' of hallucinogenic drug taking may be a poor match for the human experience. Although data chronicling year-to-year changes in the prevalence of use of the classical hallucinogens in humans are plentiful (see, for example, Drug Abuse Warning Network, 2002), more specific data on patterns of individual use are scarce. Nonetheless, it seems reasonable to assert that use patterns for the hallucinogens in humans are less robust than for other drugs of abuse, such as cocaine or heroin. Indeed, reports of hallucinogen 'bingeing' or 'craving', two concepts considered by many to be critical to addiction, are almost unknown, and the prevalence of lifetime use among some groups has remained relatively constant since 1975 (Johnston *et al.*, 2003). Thus, the use patterns of hallucinogens in humans may be compatible with the present data and indicative of the type of 'transient' reinforcing effects described herein. A more careful and thorough survey of both human and animal patterns of hallucinogen self-administration could potentially reveal important similarities or differences across species.

The finding that experience with the reinforcing effects of MDMA did not predispose any animals to reliably self-administer these hallucinogenic compounds is interesting, although inconclusive in the absence of more complete studies. Indeed, the instances of transient reinforcing effects, though limited in occurrence, may still critically depend on prior drug history. A more extensive manipulation of drug history in further studies may greatly improve our understanding of the reinforcing effects of hallucinogens.

Numerous observations in other paradigms have demonstrated that MDMA and related compounds differ from

traditional hallucinogens. Important differences in structure–activity relationships (Nichols, 1986) and discriminative stimulus effects (Glennon *et al.*, 1982; Oberlender and Nichols, 1988; but see also Baker *et al.*, 1995; Baker and Taylor, 1997) have previously been noted between MDMA and traditional hallucinogens, and these findings have led to the suggestion that MDMA may produce its hallucinogen-like effects in a way that is different from the other substituted amphetamines (Nichols, 1986). Nonetheless, the actions of MDMA at 5-HT_{2A} receptors appear to be integral to the reinforcing effects of this compound (Fantegrossi *et al.*, 2002). Why 5-HT_{2A}-mediated actions do not engender reliable self-administration of the indolealkylamines and phenylisopropylamines remains unknown.

In summary, the present data provide further evidence that several hallucinogenic drugs from two distinct structural classes do not reliably maintain contingent responding in rhesus monkeys, and further extend such findings to monkeys in which MDMA had serotonergically mediated reinforcing effects. Nonetheless, certain indolealkylamines and phenylisopropylamines did appear to have transient reinforcing effects in some subjects. This pattern of sporadic self-administration may indicate that these compounds have weak reinforcing effects, or, alternatively, mixed reinforcing and aversive effects.

Acknowledgements

The authors express their gratitude for the expert technical assistance provided by Erich Doser, Deborah Huntzinger, Sarah Pilkington and Jolan Terner. Additional thanks are due to the International Study Group Investigating Drugs as Reinforcers (ISGIDAR) for their insightful comments regarding these studies (initial results of which were presented as a talk at their 2002 meeting) and to Terry Robinson and Theresa Lee at the University of Michigan Department of Psychology for their preliminary review of this manuscript (as a chapter in the doctoral thesis of W.E.F.). Finally, the editorial comments of Jack Bergman were most helpful in the preparation of this manuscript.

References

Aghajanian GK, Marek GJ (1999). Serotonin and hallucinogens. *Neuropsychopharmacology* **21**(**suppl 2**):16s–23s.

Arnold JM, Roberts DCS (1997). A critique of fixed and progressive ratio schedules used to examine the neural substrates of drug reinfrocement. *Pharmacol Biochem Behav* **57**:441–447.

Baker L, Taylor M (1997). Assessment of the MDA and MDMA optical isomers in a stimulant-hallucinogen discrimination. *Pharmacol Biochem Behav* **57**: 737–748.

Baker LE, Broadbent J, Michael EK, Matthews PK, Metosh CA, Saunders RB, *et al.* (1995). Assessment of the discriminative stimulus effects of the optical isomers of ecstasy (3,4-methylenedioxymethamphetamine; MDMA). *Behav Pharmacol* **6**:263–275.

Beardsley PM, Hayes BA, Balster RL (1990). The self-administration of MK-801 can depend upon drug-reinforcement history, and its discriminative stimululs properties are phencyclidine-like in rhesus monkeys. *J Pharmacol Exp Ther* **252**:953–959.

Bergman J, Johanson CE (1985). The reinforcing properties of diazepam under several conditions in the rhesus monkey. *Psychopharmacology (Berl)* **86**:108–113.

Berridge KC (2000). Taste reactivity: Measuring hedonic impact in infants and animals. *Neurosci Biobehav Rev* **24**:173–198.

Broadbear JH, Winger G, Woods JH (1999). Glucocorticoid-reinforced responding in the rhesus monkey. *Psychopharmacology (Berl)* **147**:46–55.

Broadbear JH, Winger G, Rice KC, Woods JH (2002). Antalarmin, a putative CRH-R1 antagonist, has transient reinforcing effects in rhesus monkeys. *Psychopharmacology (Berl)* **164**:268–276.

Deneau G, Yanagita T, Seevers M (1969). Self-administration of psychoactive substances by the monkey – a measure of psychological dependence. *Psychopharmacologia* **16**:30–48.

Drug Abuse Warning Network *The DAWN report: club drugs, 2001 update*. Washington, DC: Office of Applied Studies, Substance Abuse, and Mental Health Services Administration.

Fantegrossi WE, Ullrich T, Rice KC, Woods JH, Winger G (2002). 3,4-Methylenedioxymethamphetamine (MDMA, 'ecstasy') and its stereoisomers as reinforcers in rhesus monkeys: serotonergic involvement. *Psychopharmacology (Berl)* **161**:356–364.

Glennon RA, Young R, Rosecrans JA, Anderson GM (1982). Discriminative stimulus properties of MDA analogs. *Biol Psychiatry* **17**:807–814.

Glennon RA, Titeler M, McKenney JD (1984). Evidence for 5-HT_2 involvement in the mechanism of action of hallucinogenic agents. *Life Sci* **35**:2502–2511.

Gudelsky G, Yamamoto B, Nash J (1994). Potentiation of 3,4-methylenedioxymethamphetamine-induced dopamine release and serotonin neurotoxicity by 5-HT_2 receptor agonists. *Eur J Pharmacol* **246**:325–330.

Hiramatsu M, Cho AK (1990). Enantiomeric differences in the effects of 3,4-methylenedioxymethamphetamine on extracellular monoamines and metabolites in the striatum of freely-moving rats: an *in vivo* microdialysis study. *Neuropharmacology* **29**:269–275.

Hoffmeister F, Wuttke W (1976). Psychotropic drugs as negative reinforcers. *Pharmacol Rev* **27**:419–428.

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

Johnston LD, O'Malley PM, Bachman JG (2003). Monitoring the Future National Survey Results on Drug Use, 1975–2002, Vol. I: Secondary school students. NIH Publication No. 03-5375. Bethesda, MD: National Institute on Drug Abuse.

Kelleher RT, Morse WH (1968). Determinants of the specificity of behavioral effects of drugs. In: Jung R, Kramer K, Krayer O, Lenhartz E, Lynen F, Muralt Av, *et al.* (editors): *Reviews of Physiology, Biochemistry, and Experimental Pharmacology*. Berlin: Springer-Verlag.

Lyness W, Friedle N, Moore K (1980). Increased self-administration of D-amphetamine after destruction of 5-hydroxytryptaminergic neurons. *Pharmacol Biochem Behav* **18**:721–724.

Marona-Lewicka D, Rhee G, Sprague J, Nichols D (1996). Reinforcing effects of certain serotonin-releasing amphetamine derivatives. *Pharmacol Biochem Behav* **53**:99–105.

Morgan A, Horan B, Dewey S, Ashby C (1997). Repeated administration of 3,4-methylenedioxymethamphetamine augments cocaine's action on dopamine in the nucleus accumbens: a microdialysis study. *Eur J Pharmacol* **331**:R1–R3.

Nader MA (1998). The influence of behavioral and pharmacological history on the reinforcing effects of cocaine in rhesus monkeys. *NIDA Res Monogr* **169**:26–55.

Nichols DE (1986). Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. *J Psychoactive Drugs* **18**:305–313.

Nichols DE, Lloyd DH, Hoffman AJ, Nichols MB, Yim GKW (1982). Effects of certain hallucinogenic amphetamine analogues on the release of [^{3}H]serotonin from rat brain synaptosomes. *J Med Chem* **25**:530–534.

Oberlender R, Nichols DE (1988). Drug discrimination studies with MDMA and amphetamine. *Psychopharmacology (Berl)* **95**:71–76.

Oberlender R, Nichols DE (1990). (+)-*N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine as a discriminative stimulus in studies of 3,4-methylenedioxymethamphetamine-like behavioral activity. *J Pharmacol Exp Ther* **255**: 1098–1106.

Poling A, Bryceland J (1979). Voluntary drug self-administration by nonhumans: a review. *J Psychedelic Drugs* **11**:185–190.

Rudnick G, Wall S (1992). The molecular mechanism of [3,4-methylenedioxymethamphetamine (MDMA)]: serotonin transporters are targets for MDMA-induced serotonin release. *Proc Natl Acad Sci USA* **89**:1817–1821.

Sadzot B, Baraban JM, Glennon RA, Lyon RA, Leonhardt S, Jan CR, *et al.* (1989). Hallucinogenic drug interactions at human brain 5-HT2 receptors: implications for treating LSD-induced hallucinogenesis. *Psychopharmacology (Berl)* **98**:495–499.

Schlichting UU, Goldberg SR, Wuttke W, Hoffmeister F (1970). D-Amphetamine self-administration by rhesus monkeys with different self-administration histories. *Exerpta Medica International Congress Series* **220**:62–69.

Schmidt C, Sullivan C, Fadayel G (1994). Blockade of striatal 5-hydroxytryptamine2 receptors reduces the increase in extracellular concentrations of dopamine produced by the amphetamine analogue 3,4-methylenedioxymethamphetamine. *J Neurochem* **62**:1382–1389.

Siegel RK, Jarvik ME (1980). DMT self-administration by monkeys in isolation. *Bull Psychon Soc* **16**:117–120.

Siegel RK, Brewster JM, Jarvik ME (1974). An observational study of hallucinogen-induced behavior in unrestrained *Macaca mulatta*. *Psychopharmacologia* **40**:211–223.

Spealman RD, Goldberg SR (1978). Drug self-administration by laboratory animals: control by schedules of reinforcement. *Annu Rev Pharmacol Toxicol* **18**:313–339.

Stafford D, LeSage MG, Glowa JR (1998). Progressive-ratio schedules of drug delivery in the analysis of drug self-administration: a review. *Psychopharmacology (Berl)* **139**:169–184.

Steele TD, Nichols DE, Yim GKW (1987). Stereochemical effects of 3,4-methylenedioxymethamphetamine (MDMA) and related amphetamine derivatives on inhibition of uptake of [^{3}H]monoamines into synaptosomes from different regions of rat brain. *Biochem Pharmacol* **36**:2297–2303.

Teitler M, Leonhardt S, Appel NM, DeSouza EB, Glennon RA (1990). Receptor pharmacology of MDMA and related hallucinogens. *Ann NY Acad Sci* **600**:626–639.

White S, Harris G, Imel K, Wheaton M (1995). Inhibitory effects of dopamine and methylenedioxymethamphetamine (MDMA) on glutamate-evoked firing of nucleus accumbens and caudate/putamen cells are enhanced following cocaine self-administration. *Brain Res* **681**:167–176.

Winsauer PJ, Moerschbaecher JM (2000). Differential effects of 5-HT agonists and antagonists on the repeated acquisition and performance of response sequences in monkeys. *Behav Pharmacol* **11**:535–553.

Woods JH (1978). Behavioral pharmacology of drug self-administration In: Lipton MA, DiMascio A, Killam KF (editors): *Psychopharmacology: A Generation of Progress*. New York: Raven Press.

Yanagita T (1986). Intravenous self-administration of R(-)-cathinone and 2-amino-1-(2,5-dimethoxy-4-methyl) phenylpropane in rhesus monkeys. *Drug Alcohol Depend* **17**:135–141.

Young AM, Woods JH (1981). Maintenance of behavior by ketamine and related compounds in rhesus monkeys with different self-administration histories. *J Pharmacol Exp Ther* **218**:720–727.

Young AM, Herling S, Woods JH (1981). History of drug exposure as a determinant of drug self-administration. *NIDA Res Monogr* **37**: 75–88.