OXFORD

REGULAR RESEARCH ARTICLE

Discriminative-Stimulus Effects of Synthetic Cathinones in Squirrel Monkeys

Alison G. P. Wakeford, Alexander M. Sherwood, Thomas E. Prisinzano, Jack Bergman, Stephen J. Kohut, Carol A. Paronis

McLean Hospital, Behavioral Biology Program, Belmont, Massachusetts, USA (Drs Wakeford, Bergman, Kohut, and Paronis); Harvard Medical School, Department of Psychiatry, Boston, Massachusetts, USA (Drs Wakeford, Bergman, Kohut, and Paronis); College of Pharmacy, University of Kentucky, Lexington, Kentucky, USA (Drs Sherwood, and Prisinzano); Usona Institute, Madison, Wisconsin, USA (Dr Sherwood).

Correspondence: Alison G. P. Wakeford, PhD, Behavioral Biology Program, McLean Hospital, Harvard Medical School, 115 Mill Street, Belmont, MA 02478, USA (awakeford@mclean.harvard.edu).

Abstract

Background: Synthetic cathinones display overlapping behavioral effects with psychostimulants (e.g., methamphetamine [MA]) and/or entactogens (e.g., 3,4-methylenedioxymethaphetamine [MDMA])—presumably reflecting their dopaminergic and/or serotonergic activity. The discriminative stimulus effects of MDMA thought to be mediated by such activity have been well characterized in rodents but have not been fully examined in nonhuman primates.
Methods: The present studies were conducted to systematically evaluate the discriminative stimulus effects of 5 abused synthetic cathinones (methylenedioxypyrovalerone [MDPV], α-pyrrolidinovalerophenone [α-PVP], methcathinone [MCAT], mephedrone, and methylone) in adult male squirrel monkeys trained to distinguish intramuscular injections of MA (0.1 mg/kg; n = 4) or MDMA (0.6 mg/kg; n = 4) from vehicle.
Results: Each training drug produced dose-dependent effects and, at the highest dose, full substitution. MDMA produced predominantly vehicle-like responding in the MA-trained group, whereas the highest dose of MA (0.56 mg/kg) produced partial substitution (approximately 90% appropriate lever responding in one-half of the subjects) in the MDMA-trained group. MDPV, α-PVP, and MCAT produced full substitution in MA-trained subjects, but, at the same or higher doses, only substituted for MDMA in one-half of the subjects, consistent with primarily dopaminergically mediated interoceptive effects. In contrast, mephedrone and methylone fully substituted in MDMA-trained subjects but failed to fully substitute for the training drug in MA-trained subjects, suggesting a primary role for serotonergic actions in their interoceptive effects.
Conclusions: These findings suggest that differences in the interoceptive effects of synthetic cathinones in nonhuman primates reflect differing compositions of monoaminergic actions that also may mediate their subjective effects in humans.

Keywords: Methamphetamine, MDMA, drug-discrimination, monkeys

Introduction

The use of synthetic cathinones emerged as a societal concern within the past 2 decades when they were introduced as cheap, "legal" alternatives to common illicit street drugs (Baumann et al., 2014; Baumann and Volkow 2016). Currently, synthetic cathinones are primarily found as adulterants in, or as replacements for, methamphetamine (MA) and/or 3,4-methylen edioxymethamphetamine (MDMA) (Seely et al., 2013; Palamar et al., 2016). Synthetic cathinones have been shown to disrupt

Significance Statement

MA and MDMA share overlapping but distinct neuropharmacological actions that are thought to mediate their behavioral effects. Specifically, MDMA (nonselective/serotonin-preferring) has garnered recent interest in its prosocial effects in humans and laboratory animals, whereas MA (dopamine-preferring) does not elicit prosocial behavior. Some currently abused synthetic cathinones demonstrate neuropharmacological actions similar to those of MA or MDMA. In the present studies, first, we have systematically compared and contrasted the overlap in discriminative stimulus effects of MDMA and MA in non-human primates. Additionally, we have extended the current understanding of the pharmacology of selected synthetic cathinones (methylenedioxypyrovalerone [MDPV], α-pyrrolidinovalerophenone [α-PVP], methcathinone [MCAT], mephedrone, methylone) by characterizing their interoceptive effects in monkeys trained to discriminate either MA or MDMA from saline. Our findings demonstrate differences in the interoceptive effects of synthetic cathinones in monkeys and suggest that the distinct pharmacological actions of these compounds may mediate their subjective effects in humans.

monoaminergic function by blocking the transport of dopamine (DA) or serotonin (5HT) into presynaptic neurons or by acting as substrate to promote the neuronal release of those neurotransmitters. These neurochemical actions previously have been shown to also mediate the psychomotor stimulant and/or mood-altering effects of MA and MDMA. The effects of MA generally are considered to be predominantly dopaminergic, as it can serve as a substrate for both the DA and 5HT transporters (DAT and SERT) but is reported to be 30-fold more potent in releasing DA than 5HT (Eshleman et al., 2017; Kohut et al., 2017). MDMA also serves as a substrate for both transporters but is relatively nonselective (about sixfold more potent) in releasing 5HT compared with DA (Rothman and Baumann 2003). These differences in the dopaminergic and serotonergic relative potencies of MA and MDMA have been forwarded as a key factor in their dissimilar effects on non-conditioned behavior (respectively, psychostimulant vs "entactogen"; see Kamilar-Britt and Bedi 2015 for a review) as well as in their different effects in operant-based procedures. For example, previous studies have shown that the discriminative-stimulus effects of MA in both rodents and nonhuman primates are dopaminergically mediated (Tidey and Bergman 1998; Munzar and Goldberg 2000; Czoty et al., 2004), whereas the discriminative-stimulus effects of MDMA, studied primarily in rodents, are thought to be predominantly, though not exclusively, mediated by its serotonergic actions (Goodwin et al., 2003). Of interest, partial or asymmetric patterns of cross-substitution of MDMA with amphetamines or cocaine in drug discrimination studies in rodents have been reported repeatedly, suggesting the involvement of dopaminergic as well as serotonergic actions in the interoceptive effects of MDMA (Oberlender and Nichols 1988; Baker et al., 1995; Khorana et al., 2004; Kueh and Baker 2007).

Synthetic cathinones, structural congeners of cathinone (β-keto-amphetamine), also produce behavioral effects that likely are governed by differences in their relative potencies as indirect dopaminergic and serotonergic agonists. In this regard, the cathinones methylenedioxypyrovalerone (MDPV) and α-pyrrolidinovalerophenone (α-PVP) are monoamine transport blockers that bind the DAT—but not the SERT—with high affinity, which is reflected in their selective potency as DA transport blockers (Eshleman et al., 2013, 2017). Methcathinone (MCAT), another high-affinity DAT ligand with little affinity for the SERT, also releases DA with MA-like potency and 5HT with lesser potency than either MA or MDMA (Eshleman et al., 2017). Notwithstanding such differences in their mechanisms, MDPV, α-PVP, and MCAT all have relatively DA-selective monoaminergic actions and produce prominent MA-like psychostimulant effects (Kaminski and Griffiths, 1994; Eshleman et al., 2017; Collins et al., 2019). In contrast, both mephedrone and methylone act

as nonselective substrates for DAT and SERT, with potency and selectivity that closely resembles MDMA (Baumann et al., 2012; Eshleman et al., 2013). Both mephedrone and methylone increase extracellular release of DA and 5HT within the synaptic cleft, with greater increases found for 5HT than DA (Baumann et al., 2012). In behavioral studies, mephedrone and methylone have also been reported to produce increased sociability and social interactions in rodents, that is, entactogenic effects that reflect their MDMA-like actions (Baumann et al., 2012; Eshleman et al., 2013; Simmler et al., 2013). These findings support the view that the type of behavioral effects of novel cathinones, that is, MA-like or MDMA-like, may be forecast by the relative selectivity of their dopaminergic and/or serotonergic actions.

Differences in the monoaminergic actions of substituted cathinones also may contribute to differing types of discriminative stimulus effects. For example, whereas MCAT failed to substitute for the training drug in MDMA-trained rodents (Gatch et al., 2020), MDPV and MCAT were found to fully substitute in MA-trained subjects (Gatch et al., 2013, 2015). MDPV also produced full substitution in rodents trained on an MDMA + amphetamine drug mixture but only partial substitution in rodents trained on MDMA alone (Harvey and Baker 2016). In contrast, mephedrone and methylone have been reported to substitute in both MA-trained and MDMA-trained rodents (Gatch et al., 2013; Dolan et al., 2018), suggesting the contribution of both dopaminergic and serotonergic actions to their interoceptive effects. Of interest, notwithstanding the full substitution of mephedrone in MA-trained rodents (Gatch et al., 2013), MA was found to only partially substitute for the training drug in mephedrone-trained subjects (Varner et al., 2013). In conjunction with the inability of MA to produce MDMA-like effects in MDMA-trained subjects (discussed above), the asymmetry between MA and mephedrone further strengthens the view that MA-like discriminative-stimulus effects are predominantly mediated by a single mechanism of action (indirect dopaminergic agonism), whereas MDMA-like discriminative-stimulus effects reflect a combination of indirect dopaminergic and serotonergic agonist activity.

Although there has been considerable work describing the discriminative-stimulus effects of cathinones in MA-trained or MDMA-trained rodents, comparable studies have not yet been conducted to determine whether a similar range of MA-like and MDMA-like effects occur in a primate species. Smith et al. (2017a, 2017b) report that several cathinones—including α-PVP, MDPV, MCAT, and methylone, but not mephedrone—fully substitute for cocaine (0.32 mg/kg) in male rhesus monkeys. However, MDMA also fully substituted for cocaine in 3 of the 4 monkeys, suggesting that its discriminative-stimulus effects did not differ greatly from those of cocaine (Smith et al., 2017a).

The present experiments were conducted to further investigate the discriminative-stimulus effects of selected synthetic cathinones considered to be dopamine-preferring (α-PVP, MDPV, MCAT) or serotonin-preferring (methylone, mephedrone) by directly comparing their discriminative stimulus effects in different groups of squirrel monkeys trained to discriminate either MA or MDMA from saline. The results of these studies indicate differences in the ability of different cathinones to fully substitute for MA or MDMA in monkeys, which, in turn, may align with their dissimilar psychomotor stimulant or entactogenic effects in humans.

Methods

Subjects

Two groups of 4 adult male squirrel monkeys (*Saimiri sciureus*) were housed in a temperature- and humidity-controlled vivarium with a 12-hour-light-/-dark cycle (7 AM-7 PM) in a facility licensed by the US Department of Agriculture and in accordance with guidelines established by the National Research Council. All procedures involving the use of experimental subjects in the present studies were approved by the Institutional Animal Care and Use Committee at McLean Hospital. Throughout the present studies, all subjects had unlimited access to water in their home cage and were maintained at approximate free-feeding weights by post-session feedings of a nutritionally balanced diet consisting of high-protein primate chow (Purina Monkey Chow, St. Louis, MO); fresh fruit and environmental enrichment were provided daily. All subjects had previously served in other studies of behaviorally active drugs (e.g., cannabinoids, opioids, and stimulants) but had not been exposed to substituted cathinones prior to the present studies.

Apparatus

During experimental sessions, subjects were seated in a polycarbonate and aluminum chair (Med Associates Inc., St. Albans, VT, #ENV-601A) in a ventilated and sound-attenuating chamber. Two response levers were positioned 5.5 cm to the left and right of the center of the front panel. Each lever-press produced an audible relay click and was recorded as a response. LED stimulus lights with red covers were mounted on the front panel of the chair and 9 cm above each response lever. Before each session, a shaved portion of each subject's tail was coated with electrode gel and placed under brass electrodes for the delivery of brief, low-intensity current (200 ms; 3 mA). Experimental events and data collection were controlled by Med Associates interfacing equipment and operating software.

Behavioral Procedure

Experimental sessions were conducted daily (Monday–Friday). Subjects were previously trained to respond under a fixed-ratio (FR) 10 schedule of stimulus termination. Under this schedule, completion of 10 consecutive responses on 1 of the 2 levers turned off red stimulus lights, terminated an associated program of current delivery, and initiated a 50-second short timeout (STO) during which all lights were off and responding had no scheduled consequences. Following the STO, the red stimulus lights were re-illuminated and the FR10 schedule of stimulus termination was again in effect. After subjects responded reliably on either lever to terminate visual stimuli, they were trained to discriminate intramuscular (i.m.) injections of either MA (0.1 mg/

kg; n = 4) or MDMA (0.6 mg/kg; n = 4) from saline vehicle. During training, 1 lever was active after vehicle injection and the other was active after drug injection (MA or MDMA). Assignment of drug and saline levers was counterbalanced across subjects in each group.

Methamphetamine Discrimination Training

All subjects initially were trained to respond during sessions comprising single or multiple cycles; for reasons not related to the present study, training sessions during these experiments were conducted using a single-cycle procedure. Under this procedure, training sessions consisted of a single cycle, each comprised of a 10-minute long timeout period (LTO) during which no consequences were programmed followed by presentations of the FR10 schedule. Subjects in the MA group were injected with either MA or saline prior to each training session's onset. Following the LTO, both red stimulus lights above the levers were illuminated. Subjects could terminate the red stimulus lights and initiate the 50-second STO by completing 10 consecutive responses on the injection-appropriate lever; responses on the other lever reset the FR requirement. Current delivery was scheduled every 10 seconds until either the FR 10 was completed on the injection-appropriate lever or 40 seconds elapsed, whichever came first. When the 50-second STO elapsed, the red lights were re-illuminated, and the FR 10 schedule of stimulus termination was again in effect. Daily training sessions consisted of 20 presentations of the FR 10 schedule. A double-alternation schedule of sessions, that is, drug-drug-vehicle-vehicle, was employed throughout training, with a third drug or vehicle session programmed intermittently to avoid associations based on the regularity of the double alternation schedule.

MDMA Discrimination Training

Subjects in the MDMA group were initially trained to discriminate injections of MDMA from saline in sessions comprising a single cycle, as described above for MA discrimination. Subsequently, daily training sessions were expanded to incorporate a variable number of cycles (n = 1–4); each cycle comprised a 10-minute timeout period followed by 10 presentations of the FR10; STO 50-second schedule as described above. Either saline or 0.6 mg/kg of MDMA was administered at the onset of each 10-minute LTO, and the number of cycles during the training sessions varied randomly with the following qualifications: (1) MDMA was administered only before the last cycle of the session and (2) sessions with injections of only saline occurred periodically (approximately 25% of all sessions) to avoid invariant associations between the injection of MDMA and the last cycle of the session.

Drug Testing

Test sessions were similar to MDMA training sessions (up to 4 cycles, each comprising the LTO followed by a response period with 10 presentations of the schedule) but with the following provisos: (1) 10 consecutive responses on either lever or the elapse of 40 seconds, whichever came first, terminated the stimulus lights and initiated the STO; and (2) current was not delivered during test sessions so as to preclude possible stimulus-induced enhancement of responding. Test sessions were conducted only when overall discrimination performance was at least 90% accurate in the immediately preceding session and 4 of the last 5 sessions. In both groups, cumulative dosing procedures (Wenger 1980) were used to establish the effects of a range of test doses in a single session. Under these procedures,

graded i.m. doses of a drug were administered at the start of successive LTO periods such that each injection increased the total dose by one-quarter or one-half of log units. Doses of drugs generally ranged from those with no effect to those that fully substituted for the training drug or decreased response rates to ≥50% below control values. However, doses were not increased further when a plateau in discriminative-stimulus effects was observed or when higher doses might be expected to fully eliminate operant behavior (specifically, in experiments with MCAT or MA in MDMA-trained subjects).

Data Analysis

The 2 primary dependent measures in the present experiments were the allocation of responding to the MA- or MDMA-associated lever, expressed as percent drug-lever responding, and overall response rate. ED_{50} values, defined as the cumulative dose of each test compound that engendered 50% responding on the drug (MA or MDMA)-associated lever, were determined using nonlinear regression in GraphPad Prism version 8.03 (GraphPad Software Inc, San Diego, CA). Percent MA or MDMA-lever response was calculated by dividing the number of responses on the lever associated with the injection of MA or MDMA by the total number of responses (excluding any responses during timeout periods). Response rate in each cycle of the session was calculated by dividing the total number of responses on both levers by the total cycle time (excluding all timeout periods). Cumulative doses of drugs were considered to substitute fully for the training drug when >90% of responses occurred on the injection-appropriate lever and response rates were >0.2 responses per second. Discrimination data were not included for cumulative doses of a drug that reduced response rate to ≤0.2 responses per second.

Drugs

Injections of drug solution or saline were administered in the calf or thigh muscle in volumes of 0.2–0.5 mL/kg. d-Methamphetamine sulfate was obtained commercially (Sigma-Aldrich); 3,4-methylenedioxymethamphetamine hydrochloride was provided by the National Institute on Drug Abuse Drug Supply program. Methylenedioxypyrovalerone (MDPV), α-pyrrolidinovalerophenone (α-PVP), methcathinone (MCAT), 4-methylmethcathinone (mephedrone), and 3,4-methylenedioxy-N-methcathinone (methylone) were all racemic mixtures, provided as the corresponding hydrochloride salts, and were synthesized at the College of Pharmacy of the University of Kentucky. All cumulative doses are expressed in terms of the weight of the free base.

Results

Control MA and MDMA Discrimination

In MA-trained subjects, MA fully substituted at the training dose of 0.1 mg/kg (ED_{50}=0.04), whereas MDMA did not substitute for MA at any dose tested (Figure 1, top left panel). MA did not appreciably alter response rates, whereas the highest dose of MDMA (1.0 mg/kg) nearly eliminated responding in MA-trained subjects (Figure 1, bottom left panel). In MDMA-trained subjects, MDMA fully substituted at the training dose of 0.6 mg/kg, whereas, on average, the highest dose of MA, 0.56 mg/kg, produced similar levels of responding on the MDMA-appropriate and vehicle-appropriate response levers (Figure 1, top right panel). Of note,

2 subjects demonstrated close to 90% MDMA-appropriate responding at 0.56 mg/kg, whereas the other 2 subjects showed closer to 90% vehicle-appropriate responding. Neither MA nor MDMA altered response rates in MDMA-trained subjects (Figure 1, bottom right panel). Doses above 0.56 mg/kg MA were not tested because 1.0 mg/kg MA previously was found to produce pronounced rate-decreasing effects in approximately one-half of the subjects trained to discriminate 0.3 mg/kg MA from saline under a similar schedule of stimulus termination (Tidey and Bergman 1998).

Discriminative Stimulus Effects of Dopamine-Preferring Synthetic Cathinones

MCAT, MDPV, and α-PVP produced differing substitution profiles in MA- and MDMA-trained subjects. Averaged for the group of MA-trained subjects, MCAT, MDPV, and α-PVP produced dose-related increases in responding on the MA-appropriate lever, with full substitution in all subjects following cumulative doses of 0.32 mg/kg MCAT and MDPV and 0.1 mg/kg α-PVP (Figure 2, top left panel). Averaged for the group of MDMA-trained subjects, the highest cumulative doses of α-PVP (0.32 mg/kg), MDPV (0.32 mg/kg), and MCAT (0.56 mg/kg) produced similar levels of responding on the MDMA-appropriate and vehicle-appropriate response levers (Figure 2, top right panel). Averaged results reflect data that varied among individuals. Two subjects demonstrated closer to 90% MDMA-appropriate responding, whereas the other 2 demonstrated closer to 90% vehicle-appropriate responding for α-PVP (0.32 mg/kg) and MDPV (0.32 mg/kg). The same subjects demonstrated the same pattern of behavior for MCAT (0.32 and 0.56 mg/kg). Based on ED_{50} values for substitution by MA- and DA-preferring synthetic cathinones (Table 1), the DA-preferring cathinones demonstrated equivalent potencies in MA-trained animals (i.e., MA ≈ α-PVP ≈ MCAT ≈ MDPV). The cathinones were more potent than MA in MDMA-trained animals, reflected in a relative rank-order of potency of α-PVP ≈ MCAT ≈ MDPV > MA.

Although the highest cumulative doses of MCAT (0.32 or 0.56 mg/kg) did not alter response rates in either MDMA-trained or MA-trained subjects, respectively, the highest cumulative dose of MDPV (0.32 mg/kg) decreased response rates to an average of approximately 1 response per second or less in both groups of subjects (Figure 2, bottom panels). The highest cumulative dose of α-PVP (0.32 mg/kg), which was not studied in MA-trained subjects, also decreased response rates to an average of <1 response per second in MDMA-trained subjects (Figure 2, bottom right panel).

Discriminative Stimulus Effects of Serotonin-Preferring Synthetic Cathinones

Methylone and mephedrone exhibited substitution profiles that differed in MA-trained and MDMA-trained subjects and that were distinct from those produced by MCAT, MDPV, and α-PVP. Thus, both methylone and mephedrone produced dose-related increases in responding on the drug-appropriate lever in MDMA-trained subjects, with full substitution following the cumulative dose of 1.0 mg/kg of each cathinone (Figure 3, top right panel). In contrast, neither methylone nor mephedrone fully substituted for MA in MA-trained subjects. Averaged for the group of MA-trained subjects, the cumulative dose of 1.0 mg/kg methylone produced approximately 70% responding on the MA-appropriate lever; however, the higher cumulative dose of 1.8 mg/kg led to <50% MA-appropriate responding,
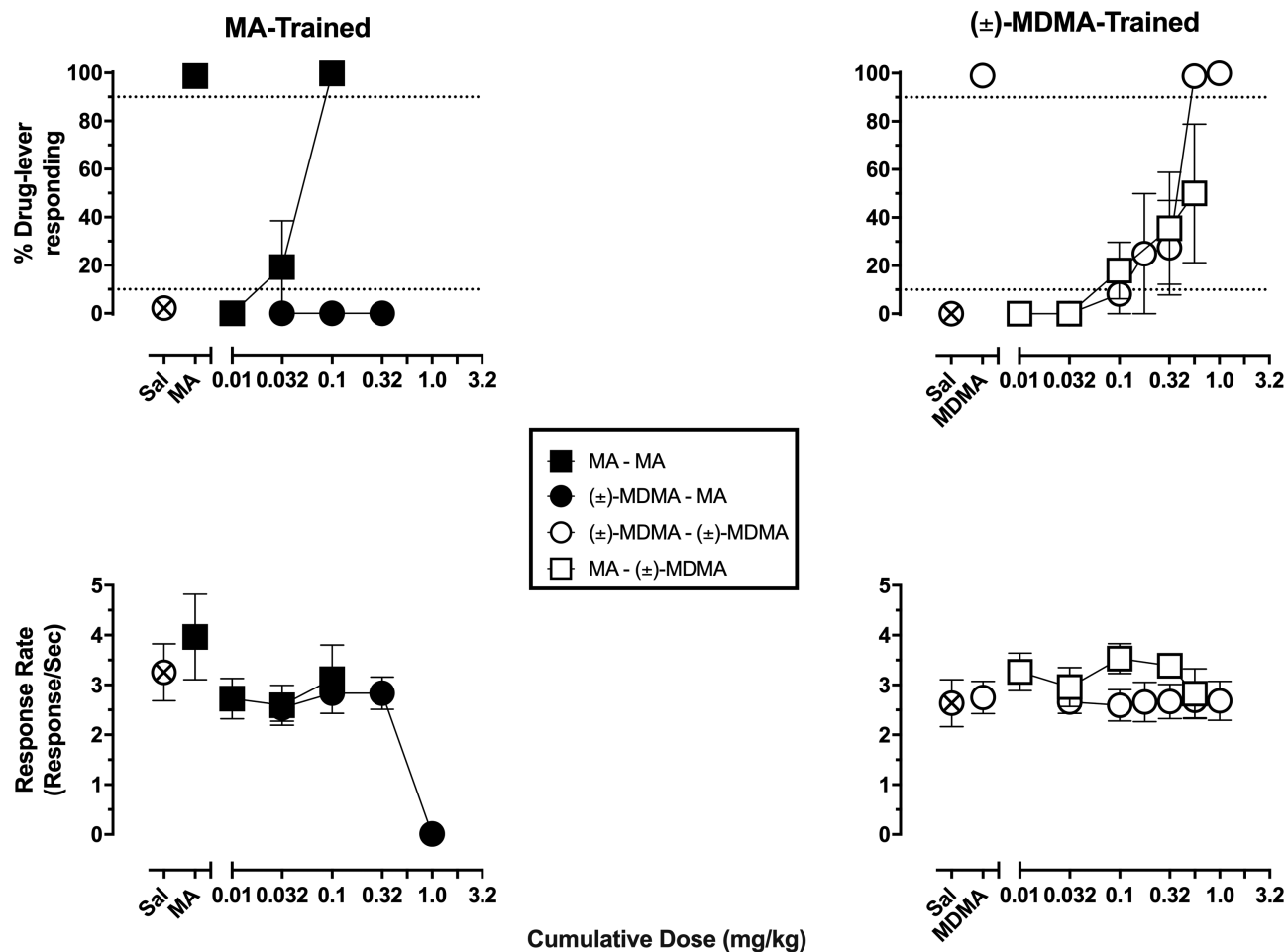
Figure 1. Average (± SEM) percent drug lever responding (top panels) and response rates (bottom panels) as a function of saline (x-circle) or cumulative doses of MA (squares) or MDMA (open circles) in methamphetamine-trained (left panel, black symbols) and MDMA-trained (right panel, white symbols) subjects.

which reflected widely varying effects among the 3 subjects in which it was studied (100% responding on the MA-appropriate lever in 1 subject and 15–20% MA-appropriate responding in the other 2 subjects; Figure 3, top left panel). The highest dose of methylone, 3.2 mg/kg, produced marked decreases in or eliminated responding in the 2 subjects in which it was studied (data not shown) and, consequently, further experiments with methylone were discontinued. Cumulative doses of mephedrone failed to produce appreciable responding (averaging <20%) on the MA-appropriate lever (Figure 3, top left panel). Based on ED_{50} values for substitution in the 2 groups of subjects (Table 1), the relative rank-order of potency for 5HT-preferring synthetic cathinones in MDMA-trained animals were MDMA > mephedrone ≈ methylone. Although ED_{50} values for MDMA or mephedrone could not be determined in MA-trained animals, the ED_{50} value for methylone was comparable with the value obtained in MDMA-trained subjects (0.71 vs 0.63 mg/kg).

The highest cumulative doses of methylone and mephedrone in MDMA-trained subjects (1.0 mg/kg) did not appreciably alter response rates. Similarly, 1.0 mg/kg methylone did not alter response rates in MA-trained subjects (Figure 3, bottom right panel). However, the cumulative dose of 1.0 mg/kg of mephedrone decreased rates of responding to an average of approximately 1 response per second or lower in MA-trained subjects (Figure 3, bottom left panel).

Discussion

Results of the present experiments indicate that MA and MDMA produce distinct and asymmetric discriminative-stimulus effects in nonhuman primates. That is, MA partly substituted in MDMA-trained subjects, whereas MDMA failed to reproduce the effects of MA in MA-trained subjects. The asymmetric cross-substitution between the discriminative-stimulus effects of MA and MDMA is consistent with the idea that their behavioral effects are mediated through dissimilar neurochemical mechanisms, that is, those of MA predominantly reflect its indirect dopamine-selective agonist actions, whereas those of MDMA reflect its nonselective dopaminergic and serotonergic actions (Kehr et al., 2011; Baumann et al., 2012, 2013; Cozzi et al., 2013; Schindler et al., 2016; Suyama et al., 2016).

Despite strong evidence for dopaminergic mediation of the discriminative-stimulus effects of MA, its ability to engender a moderate level of MDMA-appropriate responding, albeit at a relatively high dose (0.56 mg/kg), suggests the emergence of some serotonergic activity and, concomitantly, "MDMA-like" properties. This is consistent with previous findings that 2 mg/kg MA fully substituted in rodents trained to discriminate 1.5 mg/kg MDMA from saline (Gatch et al., 2020), although these doses also produced rate-decreasing effects. Similarly, high doses of MA in humans may promote a sense of well-being and pro-social behavior—effects that are often associated with MDMA
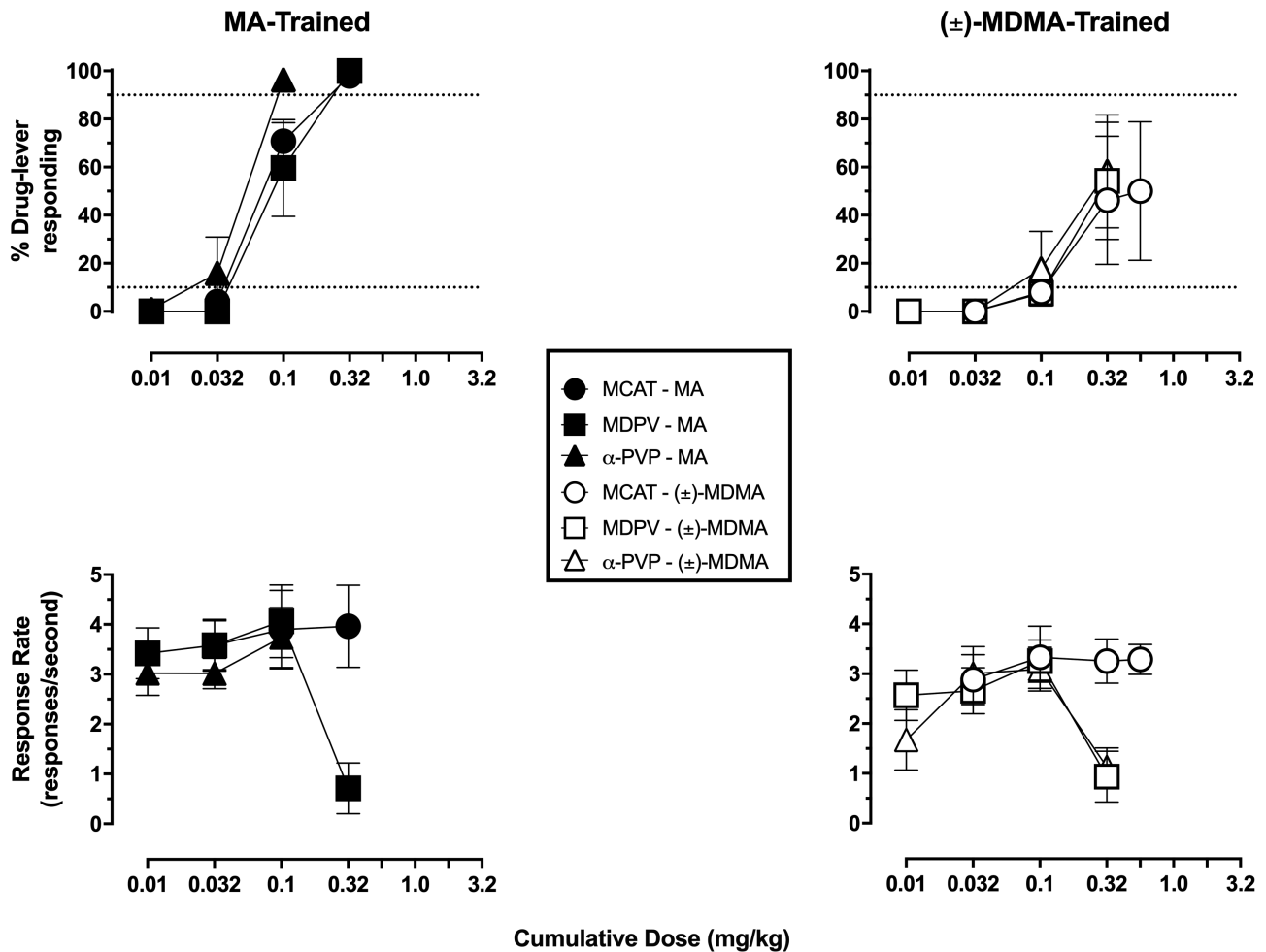
Figure 2. Average (±SEM) percent drug lever responding (top panels) and response rates (bottom panels) as a function of cumulative doses of MCAT (circles) MDPV (squares) or α-PVP (triangles) in methamphetamine-trained (left panels, black symbols) and MDMA-trained (right panels, white symbols) subjects.

Table 1. Average (±SEM) Percent Drug Lever Responding and ED_{50} (95% Confidence Level) Values for MA, MDMA, MCAT, MDPV, α-PVP, Methylone, and Mephedrone in MA-trained (top) and MDMA-trained (bottom) subjects

		MA	MDMA	MCAT	MDPV	α - PVP	Methylone	Mephedrone
MA- trained	% Drug lever responding	100 ± 0%	0 ± 0%	98 ± 2%	100 ± 0%	96 ± 2%	76 ± 9%	18 ± 18%
	ED_{50} mg/kg (95% CL)	0.04 (0.002, 0.67)	n.d.	0.08 (0.06, 0.09)	~0.10 (very wide*)	0.05 (0.03, 0.07)	0.71 (0.39, 1.32)	n.d.
MDMA-trained	% Drug lever responding	50 ± 29%	99 ± 1%	50 ± 29%	54 ± 24%	58 ± 24%	97 ± 2%	96 ± 3%
	ED_{50} mg/kg (95% CL)	0.67 (0.11, 4.16)	0.19 (0.10, 0.39)	0.28 (0.11, 0.71)	0.29 (0.20, 0.44)	0.26 (0.14, 0.47)	0.63 (0.42, 0.95)	0.56 (0.30, 1.02)

Abbreviations: MA, methamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; MCAT, methcathinone; MDPV, methylenedioxypyrovalerone; α-PVP, alpha-pyrrolidinovalerophenone.

ED_{50} represents the dose that engendered 50% responding on the MA or MDMA-associated lever.

*Note that GraphPad Prism denotes "very wide" confidence limits for data that do not unambiguously define the parameters. Many sets of parameters generate curves that fit the data equally well.

(see Kamilar-Britt and Bedi 2015). Unlike MA in MDMA-trained subjects, MDMA failed to produce any drug-appropriate effects in MA-trained subjects in the present experiments. These findings contrast with those in recent cocaine-discrimination studies in which MDMA produced complete substitution for cocaine in 3 of 4 monkeys (Smith et al., 2017a). The reason for such differing results with MA and cocaine are unclear but may reflect differences in indirect mechanisms and selectivity of neurochemical action (DA-preferring monoamine releaser vs nonselective monoamine transport blocker, respectively). Alternatively, these differences may be related to the training doses of MA and cocaine in the 2 studies. In this regard, Smith et al. (2017a) report
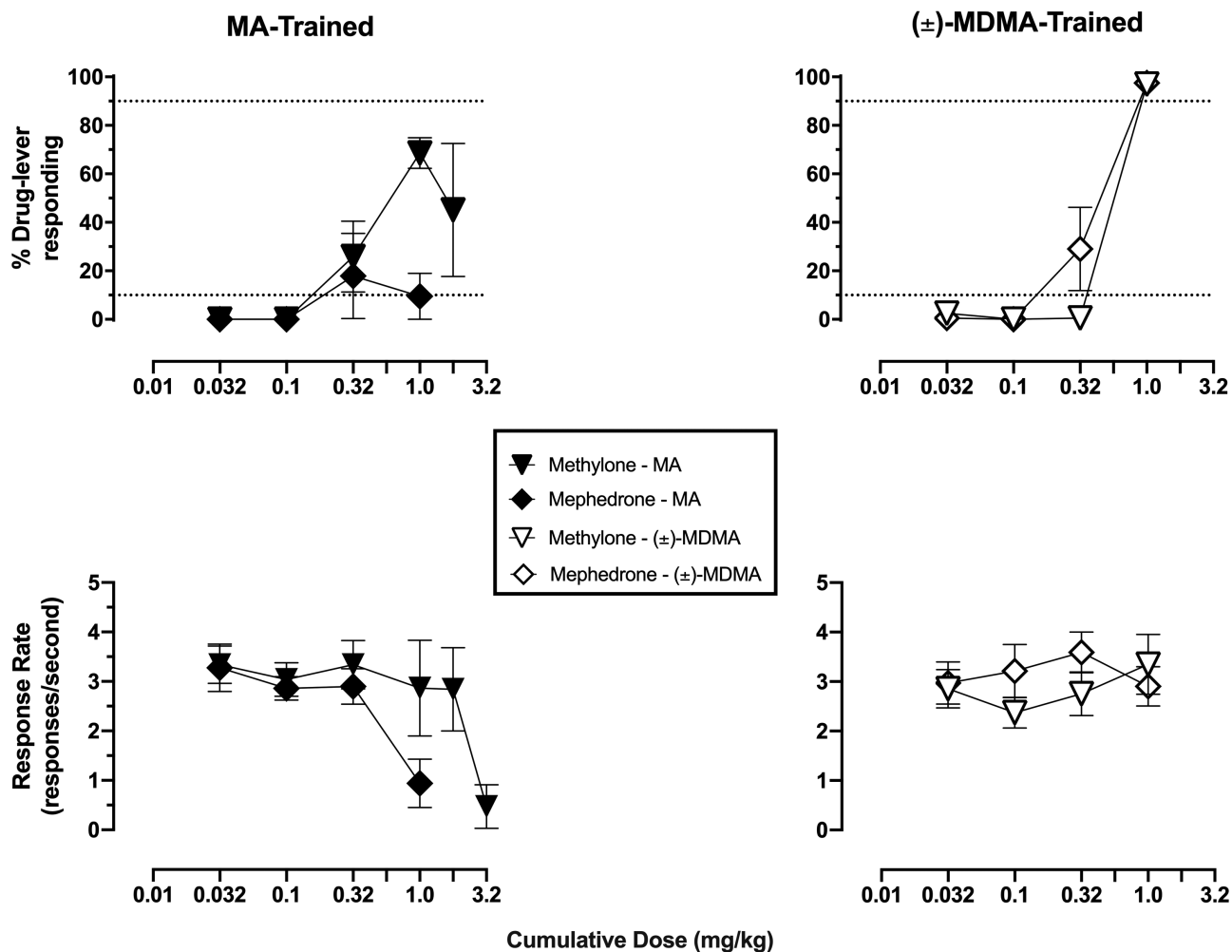
MA-Trained

(±)-MDMA-Trained

Figure 3. Average (±SEM) percent drug lever responding (top panels) and response rates (bottom panels) as a function of cumulative doses of methylone (upside down triangles) or mephedrone (diamonds) in methamphetamine-trained (left panels, black symbols) and MDMA-trained (right panels, white symbols) subjects.

full substitution for the training dose of cocaine (0.32 mg/kg) by 0.3 mg/kg MA, which is threefold higher than the training dose of MA (0.1 mg/kg) used in the present studies. Taken together, MDMA substitution for a relatively high training dose of cocaine and the MDMA-like effects of a high dose of MA (0.56 mg/kg; discussed above) suggest that MDMA might more readily produce MA-like effects in subjects trained with a higher dose of MA. Thus, while the discriminative-stimulus effects of MA and MDMA appear to be separable, they also can overlap to an extent that may depend greatly on training dose. These findings are generally consistent with previous reports. For example, the 5HT2a receptor antagonists MDL-100,907 and pirenpirone (Goodwin and Baker 2000; Goodwin et al., 2003) were found to only partially block MDMA's discriminative stimulus in rodents trained to discriminate 1.5 mg/kg MDMA from saline, whereas the D1 receptor antagonist SCH 23390, which also has high affinity for 5HT2c receptors (Millan et al., 2001), was shown to block MDMA's discriminative stimulus in rodents trained to discriminate 1.0 mg/kg MDMA from saline (Bubar et al., 2004). Of interest, however, Schenk and Highgate (2019), using a higher MDMA training dose (3.0 mg/kg), have recently reported that neither the DA antagonists SCH 23390 (D1) and eticlopride (D2) nor the 5HT antagonists ritanserin (5HT2a), WAY-100635 (5HT1a), or GR129375 (5HT1b) alone were able to alter MDMA's discriminative stimulus. Further studies with receptor-selective antagonists are needed to permit a closer evaluation of how differences in the neurochemical actions of differing training doses of MA and MDMA might contribute to separability or overlap in their discriminative-stimulus effects.

The differing dopaminergic and serotonergic actions that mediate the discriminative-stimulus effects of MA and MDMA also may underlie other behaviorally dissimilar effects that have led to their characterization as, respectively, psychomotor stimulant and entactogenic drugs. Thus, in laboratory animals, MA increases motoric activity, heightens vigilance, and serves as a strong reinforcing stimulus, whereas MDMA, via its serotonergic actions, engenders prosocial effects and thereby increases affiliative behavior (see review by Kamilar-Britt and Bedi 2015). Such behavioral distinctions between psychomotor stimulant and entactogenic drugs can be observed in laboratory animals and are highlighted in reports showing that doses of MDMA, but not MA (or, in previous studies, d-amphetamine), produced dose-dependent increases in affiliative behavior (i.e., huddling) and vocalizations in male squirrel monkeys (Miczek et al., 1981, 1982; Pitts et al., 2017). It is noteworthy that, excluding prosocial effects that may contribute to its widespread recreational use in humans, MDMA, unlike MA, does not engender consistent and/or high rates of intravenous self-administration, a preclinical model often used to examine the reinforcing effects of drugs in rodents or nonhuman primates

(Fantegrossi et al., 2002; Schenk et al., 2007; Creehan et al., 2015; de Moura et al., 2021; for a review, see Schenk 2009). These observations support the view that dopaminergic actions are prominently involved in the reinforcing effects of psychoactive drugs and, in conjunction with the present results, highlight the value of procedures such as drug discrimination that can be used to identify drugs in which such neurochemical actions play a critical behavioral role.

Each of the synthetic cathinones fully substituted for either MA or MDMA in a manner that reflected their predominant neurochemical actions. Thus, the dopamine-preferring cathinones MDPV, MCAT, and α-PVP fully substituted for MA, whereas the serotonin-preferring cathinones methylone and mephedrone fully substituted for MDMA. Most cathinones also displayed some overlap in their discriminative-stimulus properties, with MDPV, MCAT, and α-PVP producing predominantly MDMA-appropriate responding in one-half of the MDMA-trained animals and methylone, but not mephedrone, producing predominantly MA-appropriate responding in one-half of the MA-trained animals. Excepting the effects of methylone in MA-trained subjects, the propensity of cathinones to engender patterns of overlapping substitution in the 2 groups of monkeys varied considerably among subjects. As with MA in MDMA-trained subjects, such individual differences preclude general conclusions regarding the extent to which MDMA-like actions contribute to the discriminative-stimulus effects of dopamine-preferring cathinones or the extent to which MA-like actions contribute to the discriminative-stimulus effects of serotonin-preferring cathinones. Nevertheless, the present results are consistent with the idea that synthetic cathinones produce discriminative stimulus effects in nonhuman primates that are predominantly dopaminergic or serotonergic and, as in rodents, also display some overlap that may reflect a combination of dopaminergic and serotonergic neurochemical actions (e.g., Dal Cason 1997; Harvey and Baker 2016; Dolan et al., 2018; Gatch et al., 2020).

While the magnitude of substitution by methylone for MA in the present studies was similar to that reported in previous studies in rodents (approximately 70–80%), the absence of MA-like effects of mephedrone in monkeys contrasts with previous data showing that it fully substituted for MA in rodents (Gatch et al., 2013; Dolan et al., 2018). Possibly the effects of mephedrone, in particular, differ qualitatively in rodents and nonhuman primates. However, it is more likely that differing aspects of the particular studies contributed to the dissimilar results. For example, as discussed above with regard to the role of training dose in overlapping discriminative-stimulus effects of MA and MDMA, a higher training dose of MA may have resulted in more evidence of overlapping effects of mephedrone and MA in the present studies. In this regard, however, it is noteworthy that the dose of mephedrone that substituted for MDMA in rodents also produced rate-decreasing effects, whereas in the present studies, rate-decreasing effects of mephedrone were evident in the absence of substantial MA-like discriminative-stimulus effects. Finally, Smith et al. (2017a, 2017b) have previously reported that selected cathinones (α-PVP, MDPV, methylone, MCAT but not mephedrone) produce consistent drug-like discriminative-stimulus effects in monkeys trained to discriminate cocaine (0.32 mg/kg) from vehicle. Similarly, Kohut et al., (2013) showed that 0.1 mg/kg MCAT substituted in rhesus monkeys trained to discriminate 0.4 mg/kg cocaine from saline. Such consistency in the results of drug discrimination studies

in cocaine-trained and MA-trained subjects might be expected in view of the shared dopaminergic actions of cocaine and MA (albeit via differing indirect mechanisms) and the many studies suggesting symmetric overlap in their discriminative-stimulus properties (Garza and Johanson 1983; Smith et al., 2017a).

The reinforcing effects of MA, MDMA, and synthetic cathinones differ substantively in i.v. drug self-administration studies, likely reflecting differences in their neurochemical actions and related pharmacological profiles. For example, each of the synthetic cathinones studied here have been previously shown to maintain i.v. self-administration behavior in rodents (Hadlock et al., 2011; Aarde et al., 2013; Creehan et al., 2015; Gannon et al., 2017; Dolan et al., 2018). Yet, in self-administration studies that directly compared the reinforcing effects of methylone (MDMA-like) and MDPV (MA-like) in rats, methylone appeared to exhibit lesser reinforcing strength than MDPV (Schindler et al., 2016; Gannon et al., 2019), whereas, in more recent studies, methylone and MDPV demonstrated similar reinforcing strengths in rhesus macaques (de Moura et al., 2021). Similar comparisons in nonhuman primates have not been made with mephedrone, the other MDMA-like cathinone studied here. However, in comparative self-administration studies in rats with methylone and MDMA, mephedrone was found to maintain the highest intake among the 3 compounds (Creehan et al., 2015). Furthermore, it is noteworthy that self-administration of MDMA itself has been reported to be highly variable in rodents, leading to the view that its reinforcing strength also is below that of other, more selectively dopaminergic drugs (Schenk et al., 2007; Creehan et al., 2015 for a review, see Schenk 2009). Based on previous studies of the reinforcing effects of drugs with differing proportions of dopaminergic and serotonergic actions, it seems likely that the apparently lesser reinforcing strength of methylone and MDMA, at least, may be attributed to the influence of their more prominent serotonergic actions (Wee et al., 2005). Along the same lines, the greater reinforcing strength of MA and MA-like cathinones likely can be attributed to greater dopaminergic selectivity in their neurochemical actions (Kaminski and Griffiths 1994; Kehr et al., 2011; Baumann et al., 2012, 2013; Watterson et al., 2014; Gannon et al., 2017; Collins et al., 2019).

In summary, the present findings suggest that MDMA and MA share overlapping interoceptive effects in nonhuman primates and that the propensity for synthetic cathinones to substitute for a MDMA or MA discriminative stimulus is largely, but not exclusively, predicated on their monoaminergic selectivity, that is, dopaminergic vs serotonergic. Additionally, the present findings support the view that the discriminative-stimulus effects of synthetic cathinones and, more generally, psychomotor stimulants can serve as a predictor of their reinforcing effects in laboratory animals and, in turn, their abuse potential in humans.

Statement of Interest

None of the authors have any conflicts of interest to declare.

References

Aarde SM, Angrish D, Barlow DJ, Wright MJ Jr, Vandewater SA, Creehan KM, Houseknecht KL, Dickerson TJ, Taffe MA (2013) Mephedrone (4-methylmethcathinone) supports intravenous self-administration in Sprague-Dawley and Wistar rats. Addict Biol 18:786–799.

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

Baumann MH, Ayestas MA Jr, Partilla JS, Sink JR, Shulgin AT, Daley PF, Brandt SD, Rothman RB, Ruoho AE, Cozzi NV (2012) The designer methcathinone analogs, mephedrone and methylone, are substrates for monoamine transporters in brain tissue. Neuropsychopharmacology 37:1192–1203.

Baumann MH, Bukhari MO, Lehner KR, Anizan S, Rice KC, Concheiro M, Huestis MA (2017) Neuropharmacology of 3,4-methylenedioxypyrovalerone (MDPV), its metabolites, and related analogs. Curr Top Behav Neurosci 32:93–117.

Baumann MH, Partilla JS, Lehner KR, Thorndike EB, Hoffman AF, Holy M, Rothman RB, Goldberg SR, Lupica CR, Sitte HH, Brandt SD, Tella SR, Cozzi NV, Schindler CW (2013) Powerful cocaine-like actions of 3,4-methylenedioxypyrovalerone (MDPV), a principal constituent of psychoactive 'bath salts' products. Neuropsychopharmacology 38:552–562.

Baumann MH, Solis E Jr, Watterson LR, Marusich JA, Fantegrossi WE, Wiley JL (2014) Baths salts, spice, and related designer drugs: the science behind the headlines. J Neurosci 34:15150–15158.

Baumann MH, Volkow ND (2016) Abuse of new psychoactive substances: threats and solutions. Neuropsychopharmacology 41:663–665.

Bubar MJ, Pack KM, Frankel PS, Cunningham KA (2004) Effects of dopamine D1- or D2-like receptor antagonists on the hypermotive and discriminative stimulus effects of (+)-MDMA. Psychopharmacology 173:326–336.

Collins GT, Sulima A, Rice KC, France CP (2019) Self-administration of the synthetic cathinones 3,4-methylenedioxypyrovalerone (MDPV) and α-pyrrolidinopentiophenone (α-PVP) in rhesus monkeys. Psychopharmacology (Berl) 236:3677–3685.

Cozzi NV, Brandt SD, Daley PF, Partilla JS, Rothman RB, Tulzer A, Sitte HH, Baumann MH (2013) Pharmacological examination of trifluoromethyl ring-substituted methcathinone analogs. Eur J Pharmacol 699:180–187.

Creehan KM, Vandewater SA, Taffe MA (2015) Intravenous self-administration of mephedrone, methylone and MDMA in female rats. Neuropharmacology 92:90–97.

Czoty PW, Ramanathan CR, Mutschler NH, Makriyannis A, Bergman J (2004) Drug discrimination in methamphetamine-trained monkeys: effects of monoamine transporter inhibitors. J Pharmacol Exp Ther 311:720–727.

Dal Cason TA, Young R, Glennon RA (1997) Cathinone: an investigation of several N-alkyl and methylenedioxy-substituted analogs. Pharmacol Biochem Behav 58:1109–1116.

de Moura FB, Sherwood A, Prisinzano TE, Paronis CA, Bergman J, Kohut SJ (2021) Reinforcing effects of synthetic cathinones in rhesus monkeys: dose-response and behavioral economic analyses. Pharmacol Biochem Behav 202:173112.

Dolan SB, Chen Z, Huang R, Gatch MB (2018) "Ecstasy" to addiction: mechanisms and reinforcing effects of three synthetic cathinone analogs of MDMA. Neuropharmacology 133:171–180.

Eshleman AJ, Wolfrum KM, Hatfield MG, Johnson RA, Murphy KV, Janowsky A (2013) Substituted methcathinones differ in transporter and receptor interactions. Biochem Pharmacol 85:1803–1815.

Eshleman AJ, Wolfrum KM, Reed JF, Kim SO, Swanson T, Johnson RA, Janowsky A (2017) Structure-activity relationships of substituted cathinones, with transporter binding, uptake, and release. J Pharmacol Exp Ther 360:33–47.

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 161:356–364.

Gannon BM, Rice KC, Collins GT (2017) Reinforcing effects of abused 'bath salts' constituents 3,4-methylenedioxypyrovalerone and α-pyrrolidinopentiophenone and their enantiomers. Behav Pharmacol 28:578–581.

Gannon BM, Mesmin MP, Sulima A, Rice KC, Collins GT (2019) Behavioral economic analysis of the reinforcing effects of "bath salts" mixtures: studies with MDPV, methylone, and caffeine in male Sprague-Dawley rats. Psychopharmacology (Berl) 236:1031–1041.

Garza RD, Johanson CE (1983) The discriminative stimulus properties of cocaine in the rhesus monkey. Pharmacol Biochem Behav 19:145–148.

Gatch MB, Taylor CM, Forster MJ (2013) Locomotor stimulant and discriminative stimulus effects of 'bath salt' cathinones. Behav Pharmacol 24:437–447.

Gatch MB, Dolan SB, Forster MJ (2015) Comparative behavioral pharmacology of three pyrrolidine-containing synthetic cathinone derivatives. J Pharmacol Exp Ther 354:103–110.

Gatch MB, Dolan SB, Forster MJ (2020) Methylenedioxymethamphetamine-like discriminative stimulus effects of seven cathinones in rats. Behav Pharmacol 31:378–384.

Goodwin AK, Baker LE (2000) A three-choice discrimination procedure dissociates the discriminative stimulus effects of d-amphetamine and (+/–)-MDMA in rats. Exp Clin Psychopharmacol 8:415–423.

Goodwin AK, Pynnonen DM, Baker LE (2003) Serotonergic-dopaminergic mediation of MDMA's discriminative stimulus effects in a three-choice discrimination. Pharmacol Biochem Behav 74:987–995.

Hadlock GC, Webb KM, McFadden LM, Chu PW, Ellis JD, Allen SC, Andrenyak DM, Vieira-Brock PL, German CL, Conrad KM, Hoonakker AJ, Gibb JW, Wilkins DG, Hanson GR, Fleckenstein AE (2011) 4-Methylmethcathinone (mephedrone): neuropharmacological effects of a designer stimulant of abuse. J Pharmacol Exp Ther 339:530–536.

Harvey EL, Baker LE (2016) Differential effects of 3,4-methylenedioxypyrovalerone (MDPV) and 4-methylmethcathinone (mephedrone) in rats trained to discriminate MDMA or a d-amphetamine + MDMA mixture. Psychopharmacology (Berl) 233:673–680.

Kamilar-Britt P, Bedi G (2015) The prosocial effects of 3,4-methylenedioxymethamphetamine (MDMA): controlled studies in humans and laboratory animals. Neurosci Biobehav Rev 57:433–446.

Kaminski BJ, Griffiths RR (1994) Intravenous self-injection of methcathinone in the baboon. Pharmacol Biochem Behav 47:981–983.

Kehr J, Ichinose F, Yoshitake S, Goiny M, Sievertsson T, Nyberg F, Yoshitake T (2011) Mephedrone, compared with MDMA (ecstasy) and amphetamine, rapidly increases both dopamine and 5-HT levels in nucleus accumbens of awake rats. Br J Pharmacol 164:1949–1958.

Khorana N, Pullagurla MR, Young R, Glennon RA (2004) Comparison of the discriminative stimulus effects of 3,4-methylenedioxymethamphetamine (MDMA) and cocaine: asymmetric generalization. Drug Alcohol Depend 74:281–287.

Kohut SJ, Fivel PA, Blough BE, Rothman RB, Mello NK (2013) Effects of methcathinone and 3-Cl-methcathinone (PAL-434) in cocaine discrimination or self-administration in rhesus monkeys. Int J Neuropsychopharmacol 16:1985–1998.

Kohut SJ, Jacobs DS, Rothman RB, Partilla JS, Bergman J, Blough BE (2017) Cocaine-like discriminative stimulus effects of "norepinephrine-preferring" monoamine releasers: time course and interaction studies in rhesus monkeys. Psychopharmacology 234:3455–3465.

Kueh D, Baker LE (2007) Reinforcement schedule effects in rats trained to discriminate 3,4-methylenedioxymethamphetamine (MDMA) or cocaine. Psychopharmacology 189:447–457.

Miczek KA, Woolley J, Schlisserman S, Yoshimura H (1981) Analysis of amphetamine effects on agonistic and affiliative behavior in squirrel monkeys (Saimiri sciureus). Pharmacol Biochem Behav 14 (Suppl 1):103–107.

Miczek KA, Yoshimura H (1982) Disruption of primate social behavior by d-amphetamine and cocaine: differential antagonism by antipsychotics. Psychopharmacology 76:163–171.

Millan MJ, Newman-Tancredi A, Quentric Y, Cussac D (2001) The "selective" dopamine D1 receptor antagonist, SCH23390, is a potent and high efficacy agonist at cloned human serotonin2C receptors. Psychopharmacology 156:58–62.

Munzar P, Goldberg SR (2000) Dopaminergic involvement in the discriminative-stimulus effects of methamphetamine in rats. Psychopharmacology 148:209–216.

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

Palamar JJ, Salomone A, Vincenti M, Cleland CM (2016) Detection of "bath salts" and other novel psychoactive substances in hair samples of ecstasy/MDMA/"Molly" users. Drug Alcohol Depend 161:200–205.

Pitts EG, Minerva AR, Chandler EB, Kohn JN, Logun MT, Sulima A, Rice KC, Howell LL (2017) 3,4-Methylenedioxymethamphetamine increases affiliative behaviors in squirrel monkeys in a serotonin 2a receptor-dependent manner. Neuropsychopharmacology 42:1962–1971.

Rothman RB, Baumann MH (2003) Monoamine transporters and psychostimulant drugs. Eur J Pharmacol 479:23–40.

Schenk S (2009) MDMA self-administration in laboratory animals: a summary of the literature and proposal for future research. Neuropsychobiology 60:130–136.

Schenk S, Hely L, Lake B, Daniela E, Gittings D, Mash DC (2007) MDMA self-administration in rats: acquisition, progressive ratio responding and serotonin transporter binding. Eur J Neurosci 26:3229–3236.

Schenk S, Highgate Q (2019) Dopamine and serotonin antagonists fail to alter the discriminative stimulus properties of ±methylenedioxymethamphetamine. Behav Pharmacol 30:327–334.

Schindler CW, Thorndike EB, Goldberg SR, Lehner KR, Cozzi NV, Brandt SD, Baumann MH (2016) Reinforcing and neurochemical effects of the "bath salts" constituents 3,4-methylenedioxypyrovalerone (MDPV) and 3,4-methylenedioxy-N-methylcathinone (methylone) in male rats. Psychopharmacology 233:1981–1990.

Seely KA, Patton AL, Moran CL, Womack ML, Prather PL, Fantegrossi WE, Radominska-Pandya A, Endres GW, Channell KB, Smith NH, McCain KR, James LP, Moran JH (2013) Forensic investigation of K2, Spice, and "bath salt" commercial preparations: a three-year study of new designer drug products containing synthetic cannabinoid, stimulant, and hallucinogenic compounds. Forensic Sci Int 233:416–422.

Simmler LD, Buser TA, Donzelli M, Schramm Y, Dieu LH, Huwyler J, Chaboz S, Hoener MC, Liechti ME (2013) Pharmacological characterization of designer cathinones in vitro. Br J Pharmacol 168:458–470.

Smith DA, Blough BE, Banks ML (2017a) Cocaine-like discriminative stimulus effects of amphetamine, cathinone, methamphetamine, and their 3,4-methylenedioxy analogs in male rhesus monkeys. Psychopharmacology 234:117–127.

Smith DA, Negus SS, Poklis JL, Blough BE, Banks ML (2017b) Cocaine-like discriminative stimulus effects of alpha-pyrrolidinovalerophenone, methcathinone and their 3,4-methylenedioxy or 4-methyl analogs in rhesus monkeys. Addict Biol 22:1169–1178.

Suyama JA, Sakloth F, Kolanos R, Glennon RA, Lazenka MF, Negus SS, Banks ML (2016) Abuse-related neurochemical effects of para-substituted methcathinone analogs in rats: microdialysis studies of nucleus accumbens dopamine and serotonin. J Pharmacol Exp Ther 356:182–190.

Tidey JW, Bergman J (1998) Drug discrimination in methamphetamine-trained monkeys: agonist and antagonist effects of dopaminergic drugs. J Pharmacol Exp Ther 285:1163–1174.

Varner KJ, Daigle K, Weed PF, Lewis PB, Mahne SE, Sankaranarayanan A, Winsauer PJ (2013) Comparison of the behavioral and cardiovascular effects of mephedrone with other drugs of abuse in rats. Psychopharmacology (Berl) 225:675–685.

Watterson LR, Kufahl PR, Nemirovsky NE, Sewalia K, Grabenauer M, Thomas BF, Marusich JA, Wegner S, Olive MF (2014) Potent rewarding and reinforcing effects of the synthetic cathinone 3,4-methylenedioxypyrovalerone (MDPV). Addict Biol 19:165–174.

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

Wenger GR (1980) Cumulative dose-response curves in behavioral pharmacology. Pharmacol Biochem Behav 13:647–651.