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Self-administration of the synthetic cathinones 3,4-methylenedioxypyrovalerone (MDPV) and α-pyrrolidinopentiophenone (α-PVP) in rhesus monkeys

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Abstract

Rationale: The availability and abuse of synthetic analogues of cathinone have increased dramatically around the world. Synthetic cathinones, such as 3,4-methylenedioxypyrovalerone [MDPV] and α-pyrrolidinopentiophenone [α-PVP], are cocaine-like inhibitors of monoamine transporters and common constituents of “bath salts” or “flakka” preparations. Studies in rats suggest that MDPV and α-PVP are 3 to 4-fold more effective reinforcers than cocaine; however, comparisons of the relative reinforcing effectiveness of MDPV and α-PVP have not been reported in other species.

Objectives: Accordingly, in the present study, 4 adult male rhesus monkeys responding under a progressive ratio schedule of reinforcement were used to characterize the reinforcing effects of

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CONFLICT OF INTEREST STATEMENT

On behalf of all authors, the corresponding author states that there is no conflict of interest.

MDPV and α-PVP and to compare directly these effects to those of cocaine and methamphetamine.

Results: MDPV was the most potent reinforcer, followed by α-PVP, methamphetamine, and cocaine. α-PVP was the most effective reinforcer, followed by MDPV, cocaine, and methamphetamine. In addition to making more responses to obtain MDPV and α-PVP, monkeys also responded for longer periods of time when MDPV or α-PVP were available compared to when either cocaine or methamphetamine were available for infusion.

Conclusions: These studies confirm recent reports from rodents, and provide strong evidence that the synthetic cathinones MDPV and α-PVP are capable of maintaining high levels of responding for prolonged periods of time, and that they function as more effective reinforcers than either cocaine or methamphetamine. The relative strength of these reinforcing effects may account for the high rates of "bath salts" use reported in humans.

Keywords

synthetic cathinones; MDPV; α-PVP; cocaine; methamphetamine; rhesus monkey; self-administration

INTRODUCTION

Worldwide estimates suggest that the abuse of stimulant drugs (e.g., cocaine, amphetamine-type stimulants, "ecstasy") is second only to cannabinoids (UNODC, 2018). Although cocaine and methamphetamine remain the most widely used stimulant drugs, synthetic cathinones, often referred to as "bath salts" or "flakka", represent a growing, and ever evolving threat to public health. Indeed, recent estimates suggest that high school age students in the United States are more likely to use synthetic cathinones than either heroin or methamphetamine (Johnston et al. 2019; Palamar et al. 2019). The abuse of synthetic cathinones is associated with a variety of adverse effects, including abuse, excited delirium, acute psychosis, aggressive/violent behavior, cardiovascular complications, and death (Benzie et al. 2011; Spiller et al. 2011; Prosser et al. 2012; Miotto et al. 2013; Johnson and Johnson, 2014). Since their emergence in 2009, the number of synthetic cathinones identified on the world illicit drug market has increased steadily, with a total of 148 unique cathinone derivatives identified in 2017 (UNODC, 2018), 14 of which have been placed under Schedule I regulations by the United States Drug Enforcement Administration.

Similar to other stimulant drugs, synthetic cathinones exert their abuse-related and toxic effects through interactions with monoaminergic (e.g., dopamine [DAT], norepinephrine [NET], and serotonin [SERT]) transporters, where they can function as cocaine-like uptake inhibitors (e.g., 3,4-methylenedioxypyrovalerone [MDPV], or α-pyrrolidinopentiophenone [α-PVP]), or amphetamine-like substrates (e.g., 3,4-methylenedioxy-N-methylcathinone [methylone], or 4-methylmethcathinone [mephedrone]) to increase extracellular levels of dopamine, norepinephrine, and serotonin (Baumann et al. 2013; Eshleman et al. 2013, 2017; Simmler et al. 2013; Gannon et al. 2018a). Despite similarities in their mechanism of action, human users report that synthetic cathinones are powerful stimulants, with subjective effects that are similar to or greater than those produced by drugs such as cocaine and

methamphetamine (Winstock et al. 2011; Carhart-Harris et al. 2011; Johnson & Johnson, 2014). It is important to note, however, that the chemical constituents of “bath salts” and related preparations varies across “brands”, and within “brand” across time (e.g., Brandt et al. 2010; Spiller et al. 2011; Schneir et al. 2014), making it difficult for users to accurately predict which synthetic cathinone(s) they are using at any given time. Although this shifting composition likely contributes to variability in the euphoric and subjective effects reported in humans (e.g., Winstock et al. 2011; Johnson & Johnson, 2014), mounting evidence from preclinical studies suggests that the abuse-related effects (e.g., locomotor stimulatory, discriminative stimulus, and reinforcing effects) of synthetic cathinones exist on a continuum.

For instance, early studies in rodents indicated that MDPV was more effective than methamphetamine (0.05 or 0.25 mg/kg/inf) at maintaining responding under a progressive ratio (PR) schedule of reinforcement in rats (Aarde et al. 2013; Watterson et al. 2014), whereas behavioral economic studies suggest that cathinones such as methylone and 4-methyl-N-ethylcathinone (4-MEC) are less effective than cocaine or methamphetamine (Huskinson et al. 2017; Gannon et al. 2019). These findings have been confirmed and extended to clearly show that MDPV and α-PVP maintain final ratios approximately 3- to 5-fold larger, whereas methylone maintains final ratios approximately 4-fold smaller than those maintained by either cocaine or methamphetamine (Gannon et al. 2017a; 2018a; 2018b). Consistent with previous reports linking the reinforcing effects of cocaine to its potency to inhibit uptake at DAT (Ritz et al. 1987; Bergman et al. 1989), the potency of a series of structurally-related, pyrrolidine-containing cathinones (e.g., MDPV, MDPBP, α-PVP, α-PPP) to function as reinforcers is similarly correlated with their potency to inhibit uptake at DAT (Gannon et al. 2018a; 2018c). Although these findings suggest that the reinforcing effects of MDPV and related cathinones are primarily mediated by their capacity to increase dopamine signaling, their reinforcing effects appear to be negatively modulated by actions at SERT (Aarde et al. 2013; 2015; Dolan et al. 2018; Gannon et al. 2017a; 2017b; 2018a; 2018c; 2018d; Huskinson et al. 2017; Motbey et al. 2013; Watterson et al. 2014). Indeed, a recent study in rats found that the relative reinforcing effectiveness of a series of synthetic cathinones was positively correlated with their selectivity to inhibit uptake at DAT relative to SERT (Gannon et al. 2018a), strongly suggesting that the abuse potential of stimulant drugs (e.g., cocaine, methamphetamine, and synthetic cathinones) is determined by their capacity to stimulate dopamine systems, with increases in serotonergic activity serving to negatively modulate, or dampen their reinforcing effectiveness. Although a handful of studies have demonstrated that cathinone functions as a reinforcer in rhesus monkey (Schuster & Johanson, 1979; Yanagita, 1979; Johanson & Schuster, 1981; Woolverton & Johansen, 1984; Yanagita, 1986), relatively little is known about the abuse-related effects of synthetic cathinones. For instance, although a pair of studies (Smith et al. 2017a; Smith et al. 2017b) recently demonstrated that 5 common synthetic cathinones (MDPV, α-PVP, methcathinone, methylone, and mephedrone) have cocaine-like discriminative stimulus effects, as has been reported in rats (Gatch et al. 2013; 2015; Collins et al. 2016; Gannon and Fantegrossi, 2016), it is currently unclear if the differences in reinforcing effectiveness observed in rats (e.g., α-PVP > MDPV > cocaine = methamphetamine), also translate to non-human primates. Accordingly, the present studies

used a PR schedule of reinforcement to compare directly the reinforcing effects (potency and effectiveness) of two common synthetic cathinones (MDPV and α-PVP) to two widely abused stimulant drugs (cocaine and methamphetamine) in four adult male rhesus monkeys.

METHODS

Subjects.

Four adult male rhesus monkeys (7.8-11.7 kg) participated in these studies. All monkeys were individually housed in an environmentally controlled vivarium under a 14 h/10 h light/dark cycle with continuous access to water. Monkeys were fed primate chow (Harlan Teklad, High Protein Monkey Diet, Madison, WI), fresh fruit, and peanuts daily in the morning, approximately 4 h before the start of their daily experimental session. Although experimental histories differed among these monkeys, all four had a history of cocaine self-administration prior to initiating these studies. All monkeys were maintained, and all experiments were performed, in accordance with the Institutional Animal Care and Use Committee, The University of Texas Health Science Center at San Antonio, and with the Guide for the Care and Use of Laboratory Animals (National Research Council 2011).

Surgical Preparation & Apparatus

Monkeys were initially anesthetized with 10 mg/kg of ketamine (SC; Henry Schein, Dublin, OH) prior to being intubated, and maintained on 2 l/min oxygen and 2% isoflurane anesthesia (Butler Animal Health Supply, Grand Prairie, TX, USA) to allow for an indwelling venous catheter to be placed. Catheters exited the monkeys in the mid-scapular region, and monkeys were fit with a mesh primate jacket (Lomir Biomedical Inc., Malone, NY, USA) connected to a stainless steel tether through which the catheter was passed and connected to an 18-ga fluid swivel (Lomir Biomedical Inc., Malone, NY, USA). The swivel was secured to the back wall of the cage to allow free movement within the home cage. An instrument panel was located on one side of the cage which contained two or three depressible levers (Model 121-07, BRS-LVE, Laurel, Maryland, USA), separated by stainless steel dividers to reduce the likelihood of pressing multiple levers with the same hand. A stimulus light that could be illuminated red or green was located above each lever. Silicone tubing connected the swivel to an infusion pump (PHM-100; Med-Associates, Georgia, Vermont, USA) that was located behind the cage. A computer running Med-PC IV software (Med-Associates, Georgia, Vermont, USA) that was located behind the cage controlled experimental events.

Self-Administration.

Similar to previous studies performed in chaired monkeys (Gerak et al. 2016; Collins & France, 2018), the current study allowed monkeys to self-administer drug under a PR schedule of reinforcement in which the initial ratio was set to 32, and the response requirement incremented with each infusion according to the equation: ratio=[5e^(infusion number+9)*0.2)]-5). This resulted in the following series of ratio values: 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, 737, 901, etc. A catheter loading infusion was delivered approximately 1 h before the start of the session in order to fill the catheter with the appropriate concentration of the drug that would be available for responding. The

start of the session was signaled by the illumination of the green light above the active lever (counterbalanced across monkeys) which also served as the discriminative stimulus that drug infusions were available for responding on that lever. Drug infusions were delivered in conjunction with a 5-sec presentation of the red light above the active lever (i.e., infusion-associated stimuli), and followed by a 30-sec timeout during which the discriminative and infusion-associated stimuli were extinguished and responses were recorded but had no scheduled consequence. Illumination of the green light above the active lever signaled the end of the timeout, and indicated that drug was available for responding. Responses on the inactive lever were recorded but had no scheduled consequence. The maximum session duration was 20 h; however, sessions were terminated if a ratio was not completed within 2 h (i.e., 2 h limited hold). The order of testing was cocaine (0.0032-0.32 mg/kg/inf), methamphetamine (0.0032-0.1 mg/kg/inf), MDPV (0.001-0.01 mg/kg/inf), and α-PVP (0.001-0.01 mg/kg/inf). For each drug, the doses were evaluated in random order, with each dose available until the stability criterion was met (number of infusions differed by no more than 2 from day to day). Full dose-response curves for each drug were determined in duplicate before moving on the next drug. Saline served as a negative control, and was occasionally substituted for drug on at least 4 occasions to ensure that responding was being maintained by drug infusions. In order to determine if sensitivity to the reinforcing effects of cocaine was affected by the sequence of testing, the cocaine dose-response curve was determined a third time after all other dosing conditions had been evaluated.

Drugs.

(−)-Cocaine HCl was provided by the National Institute of Drug Abuse Drug Supply Program, and d-methamphetamine HCl was purchased from Sigma-Aldrich (St. Louis, MO). (+/−)-MDPV HCl, and (+/−)-α-PVP HCl were synthesized by Agnieszka Sulima and Kenner Rice at the Drug Design and Synthesis Section of the Molecular Targets and Medications Branch on the Intramural Research Programs of the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism (Bethesda, MD). All drugs were dissolved in physiologic saline, with doses expressed as the salt in mg per kg body weight.

Statistical Analyses.

At the group level, the mean number of infusions (± 1 SEM), mean final ratio, and mean session duration in minutes (± 1 SEM) are shown for each drug; variance around the mean final ratio is not reported. At the individual subject level, the mean number of infusions and final ratio completed are shown for the two determinations for each drug. Normalized PR dose-response curves were used to obtain estimates of reinforcing potency [dose estimated to produce a 50% (ED_{50}) of maximal responding for a given drug] and effectiveness [maximal number of infusions (E_{max}), regardless of dose] for individual subjects. Briefly, dose-response curves for each drug were normalized to the dose of that drug that maintained the greatest number of infusions (E_{max}), and saline (i.e., E_{max} = 100%, and infusions of saline = 0%), with ED_{50} values obtained by linear regression of the portion of the dose-response curve spanning the 20%–80% effective levels (i.e., inclusive of no more than one dose above 80% and no more than one dose below 20%). Mean ED_{50} (95% confidence intervals) provide an estimate of the reinforcing potency for a given drug, whereas mean

E_{max} values (± 1 SEM) provide a dose-independent estimate of the reinforcing effectiveness for a given drug. One-way, repeated measures ANOVA followed by post-hoc Tukey's test for multiple comparisons to determine if E_{max} values or maximum session durations varied significantly among the drugs, whereas differences in ED_{50} values were considered statistically significant if the confidence intervals did not overlap. Prism 7.04 software (GraphPad Software, Inc., La Jolla, CA) was used to generate figures and conduct statistical analyses.

RESULTS

Depicted in figure 1 are dose-response curves for the mean (± 1 SEM) data for the total number of infusions earned (figure 1; top panel) and corresponding session duration (figure 1; bottom panel) for 4 monkeys responding under a PR schedule of reinforcement for cocaine, methamphetamine, MDPV, or α-PVP. Estimates for relative reinforcing potency (ED_{50}), and dose-independent measures of relative reinforcing effectiveness (E_{max} infusions, and E_{max} final ratio), as well as the maximum session duration for each of the drugs are reported in Table 1. The rank order for potency was MDPV = α-PVP > methamphetamine > cocaine, with MDPV and α-PVP being ~4- to 5-fold more potent than cocaine, and methamphetamine being ~2.5-fold more potent than cocaine. A repeated measures, one-way ANOVA of the maximal number of infusions earned revealed a significant main effect of drug ($F[3,9] = 20.4$; $p<0.001$), with post-hoc Tukey's tests indicating that cocaine, MDPV, and α-PVP each maintained more infusions than methamphetamine, whereas α-PVP, but not MDPV, maintained significantly more infusions than cocaine at the group level. A similar relationship was observed with respect to the maximal final ratio completed, with a significant main effect of drug ($F[3,9] = 10.2$; $p<0.01$), and post-hoc tests indicating that the final ratios completed were each larger for MDPV, and α-PVP compared with methamphetamine, with the final ratio completed for α-PVP, but not MDPV, being significantly greater than for cocaine. Maximal session duration also varied as a function of the drug that was available for infusion ($F[3,9] = 6.1$; $p<0.05$), with MDPV maintaining responding for significantly longer periods of time than either cocaine or methamphetamine.

Dose-response curves for individual subject data are shown in Figure 2. Consistent with the group level data, MDPV and α-PVP tended to maintain more responding than cocaine; however, for one subject (M4), cocaine, MDPV, and α-PVP each maintained comparable levels of responding, suggesting that for this monkey they were equally effective reinforcers. It is also worth noting that even though dose-response curves for most drugs either reached asymptotes (difference in total number of infusions earned differed by less than 2 from one dose to the next), or began to display an inverted U shape (i.e., decreased responding with increasing dose), for two subjects (M2 and M3), it was not possible to accurately estimate the maximal effect level for α-PVP. Thus, rather than risk the safety of the monkeys by evaluating larger doses, infusion data from the largest dose were used to estimate the E_{max} for α-PVP. Maximal effect levels for methamphetamine, MDPV, and α-PVP were also normalized to the maximal effect of cocaine for individual subjects (1-4), and expressed change scores (Figure 3).

As shown in Table 1, the reinforcing potency and effectiveness of cocaine did not change over the course of the study with initial estimates not different from those obtained after evaluating methamphetamine, MDPV, and α-PVP in duplicate.

DISCUSSION

Studies in rodents suggest that the locomotor and discriminative stimulus effects of synthetic MDPV and α-PVP are similar to those of cocaine and methamphetamine (Marusich et al. 2012; 2014; Baumann et al. 2013; Fantegrossi et al. 2013; Aarde et al. 2013; 2015; Gatch et al. 2013; Berquist et al. 2016; 2017; Collins et al. 2016; Gannon et al. 2016); however, mounting evidence suggests that both MDPV and α-PVP function as more effective reinforcers than either cocaine or methamphetamine (Aarde et al. 2013; 2015; Watterson et al. 2014; Gannon et al. 2017a; 2018a). Although less is known about the abuse-related effect of cathinone and synthetic analogues of cathinone in rhesus monkeys, evidence suggests that the reinforcing effectiveness of cathinone is comparable to cocaine (Woolverton & Johanson, 1984), and that the discriminative stimulus effects of MDPV, α-PVP, and related synthetic cathinones overlap with those of cocaine (Smith et al. 2017a; 2017b). The current studies confirm and extend these findings by demonstrating that not only do MDPV and α-PVP function as reinforcers in rhesus monkeys, but that they are more effective than either cocaine (in 3 of 4 monkeys) or methamphetamine (in all monkeys) at maintaining responding under a PR schedule. These findings are consistent with the results of rodent studies, and anecdotal reports from humans suggesting that abuse-related effects of synthetic cathinones, such as MDPV and α-PVP, are greater than the prototypical stimulant drugs of abuse (e.g., cocaine, methamphetamine), and provide further, strong evidence that MDPV and α-PVP have particularly high abuse potential.

The current study used a PR schedule of reinforcement to quantify and compare the reinforcing effects of two common synthetic cathinones, MDPV and α-PVP, to the reinforcing effects of cocaine and methamphetamine. This schedule was chosen because it results in monotonically increasing dose-response curves for most drugs of abuse, which make it ideal for making quantitative comparisons of reinforcing potency (i.e., ED_{50}s) and reinforcing effectiveness (i.e., E_{max}) among drugs. Importantly, the relative measures of potency and effectiveness for cocaine and methamphetamine obtained in the current study align with those reported in a previous study that used this PR schedule to compare the reinforcing effects of cocaine and methamphetamine in rhesus monkeys (Lile et al. 2013). In addition, the rank order for reinforcing potency in rhesus monkeys (MDPV = α-PVP > methamphetamine > cocaine) is consistent with recent comparisons of these drugs in rats (Gannon et al. 2017a; 2018a). Although this relationship is in general agreement with their relative potency to inhibit uptake at human DAT (Eshleman et al. 2013; 2017), studies in rats have reported a larger difference in potency between MDPV and cocaine (~10-fold; Gannon et al. 2017a; 2018a) than was observed in rhesus monkeys (~5-fold). Likewise, although the rank order for reinforcing effectiveness (α-PVP >= MDPV > cocaine >= methamphetamine) is largely consistent across species, the magnitude of these differences (final ratio completed) was ~2-fold larger in rats (α-PVP ~4-fold > cocaine, MDPV ~2-fold > cocaine; Gannon et al. 2017a; 2018a) than was observed in rhesus monkeys (α-PVP ~2-fold > cocaine, MDPV ~1.5-fold > cocaine). Importantly, there are several possible explanations

for differences between the reinforcing effects of MDPV and α-PVP between rats and rhesus monkeys, including schedule constraints in the current study, differences in the functional selectivities of these drugs at DAT, NET, and SERT, and/or pharmacokinetic profiles between rats and rhesus monkeys.

First, given that the dose-response curves for MDPV and α-PVP did not reach an asymptote in 2 monkeys (M2 and M3), it is possible that the current studies underestimated the E_{max} values for MDPV and α-PVP, and that evaluation of a larger dose would have resulted in further increases in the maximum number of infusions earned (or reductions in the number of infusions as was observed at the 0.1 mg/kg/inf dose in the other monkeys). Importantly that M2 and M3 both exhibited extremely high levels of responding for the largest dose of α-PVP (28 infusions; final ratio completed = 8175) on several occasions, suggests that both monkeys could obtain more infusions than the 26 that constituted their stable effect level for 0.1 mg/kg/inf α-PVP. Although speculative, given that sessions in which large doses of MDPV and α-PVP (0.1 mg/kg/inf) were available lasted on average 18 h for monkeys M2 and M3 (compared to <7 h for E_{max} doses of cocaine or methamphetamine), it is possible that changes in sleep and/or activity interfered with our ability to capture a “true” maximal effect for MDPV and α-PVP in all monkeys. In addition, it should be pointed out that unlike monkeys M1-M3 who all responded for MDPV and α-PVP at levels significantly greater than cocaine or methamphetamine, the reinforcing effectiveness of MDPV and α-PVP appeared to be comparable to cocaine (but greater than methamphetamine) in monkey M4. Although the factors that contributed to this differential response are unknown, this finding highlights the importance of considering individual subject data when interpreting the behavioral effects of drugs. Moreover, while the schedule parameters used in the current studies appear to be well suited for evaluating drugs such as cocaine and methamphetamine, refining these procedures (e.g., larger starting ratio, more rapid increases in ratio size, shorter limited hold, etc.) may be necessary when evaluating drugs, such as MDPV and α-PVP, which appear to function as significantly more effective reinforcers. In addition, it is also possible that the use of alternative approaches for scaling reinforcing effectiveness (e.g., behavioral economic demand curve analyses) would have resulted in a more accurate assessment of the relative reinforcing effects of cocaine, methamphetamine, MDPV, and α-PVP. However, it should be pointed out that a recent study in rats used these two methods (PR and demand curve analyses) to characterize the reinforcing effects of a series of structurally related, pyrrolidine-containing synthetic cathinones (e.g., MDPV, MDPPP, α-PVP, α-PPP), and found a high degree of correlation between the estimates of reinforcing effectiveness obtained from PR schedules and demand curve analyses (Gannon et al. 2019). When taken together with the results of previous studies in rats (Aarde et al. 2013; 2015; Watterson et al. 2014; Gannon et al. 2017a; 2018a), this study provides strong evidence to suggest that α-PVP and MDPV function as exceptionally powerful reinforcers capable of maintaining significantly greater levels of responding than either cocaine or methamphetamine.

Second, although the functional profiles of MDPV and α-PVP have not been evaluated in assays expressing DAT, NET, and SERT from the rhesus monkey, differences in the relative potency and effectiveness for MDPV, α-PVP and cocaine between rats and rhesus monkeys are consistent with differences in the functional profiles obtained for rat versus human DAT,

NET, and SERT (Eshleman et al. 2013; 2017; Gannon et al. 2018a). For example, the potency difference between MDPV and cocaine to inhibit uptake at DAT is greater for rats (~65-fold; Gannon et al. 2018a) than human (~30-fold; Eshleman et al. 2013). While these difference could account for the differences in relative reinforcing potency observed between MDPV and cocaine in rats (e.g., Gannon et al. 2017a, 2018a) and rhesus monkeys, differences in the functional selectivity of MDPV to inhibit uptake at DAT relative to SERT in rats (~750-fold; Gannon et al. 2018x) and humans (~110-fold; Eshleman et al. 2013) could also account for differences in relative reinforcing effectiveness observed between rats and rhesus monkeys. Interestingly, unlike MDPV, the functional selectivity of α-PVP to inhibit uptake at DAT relative to SERT appears to be much more similar between rats (~3800-fold; Gannon et al. 2018a) and humans (~2900-fold; Eshleman et al. 2013). Thus, despite slight differences in the relative reinforcing potency and effectiveness of cocaine, methamphetamine, MDPV, and α-PVP between rats and rhesus monkeys, the current findings provide additional evidence linking reinforcing potency of stimulant drugs to their potency to inhibit uptake at DAT, and reinforcing effectiveness to their selectivity to inhibit DAT relative to SERT, as has recently been established for these drugs in rats (Gannon et al. 2018a, 2018c). Importantly, although this relationship between DAT/SERT selectivity and reinforcing effectiveness appears adequate to describe the reinforcing effects of monoamine uptake inhibitors, such as cocaine, MDPV, and α-PVP, the fact that methamphetamine was the least reinforcing drug in all four monkeys suggests that the reinforcing effectiveness of monoamine releasing drugs is influenced by other pharmacological properties (e.g., release of 5-HT).

Third, in addition to these apparent species differences in the functional profiles of MDPV and α-PVP, there is also evidence to suggest that the pharmacokinetic profiles of MDPV and α-PVP differ between rats and rhesus monkeys. For instance, when administered to rats at functionally equivalent doses, the locomotor effects of MDPV and α-PVP are similar in terms of their duration of action (Gatch et al. 2013; 2015); however, in rhesus monkeys, the discriminative stimulus effects of MDPV appear to be significantly longer lived than an equivalent dose of α-PVP (~300 versus ~60 min; Smith et al. 2017a). Although such large differences in duration of action could also account for differences in the relative reinforcing effectiveness of observed for MDPV and α-PVP (e.g., due to drug accumulation), a more rigorous evaluation of the pharmacokinetic profiles of MDPV and α-PVP in rhesus monkeys is necessary to support such claims.

In summary, synthetic cathinones represent a serious and growing threat to public health. Despite their use being linked to high levels of toxicity, and recent evidence suggesting that high school students in the United States are more likely to use synthetic cathinones, and α-PVP in particular, than either heroin or methamphetamine (Johnston et al. 2019; Palamar et al. 2019), little is known about the abuse-related effects of these drugs in non-human primates. The present study is the first to describe the reinforcing effects of MDPV and α-PVP in non-human primates, and provides a direct comparison of the relative reinforcing potency and effectiveness of these synthetic cathinones to those of the most widely used stimulant drugs of abuse, cocaine and methamphetamine. Consistent with mounting evidence from studies in rats, MDPV and α-PVP maintained significantly greater levels of responding than either methamphetamine or cocaine, suggesting that they function as

exceptionally highly effective reinforcers. Moreover, when taken together with the finding that MDPV and α-PVP were capable of maintaining these high rates of responding under the PR schedule for exceedingly long periods of time (e.g., 18-20 h), these studies provide strong evidence in support of the notion that MDPV and α-PVP have particularly high potential for abuse.

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Nonstandard abbreviations

MDPV	3,4-methylenedioxypyrovalerone
α-PVP	α-pyrrolidinopentiophenone
DAT	dopamine transporter
NET	norepinephrine transporter
SERT	serotonin transporter
PR	progressive ratio
TO	timeout
ANOVA	analysis of variance

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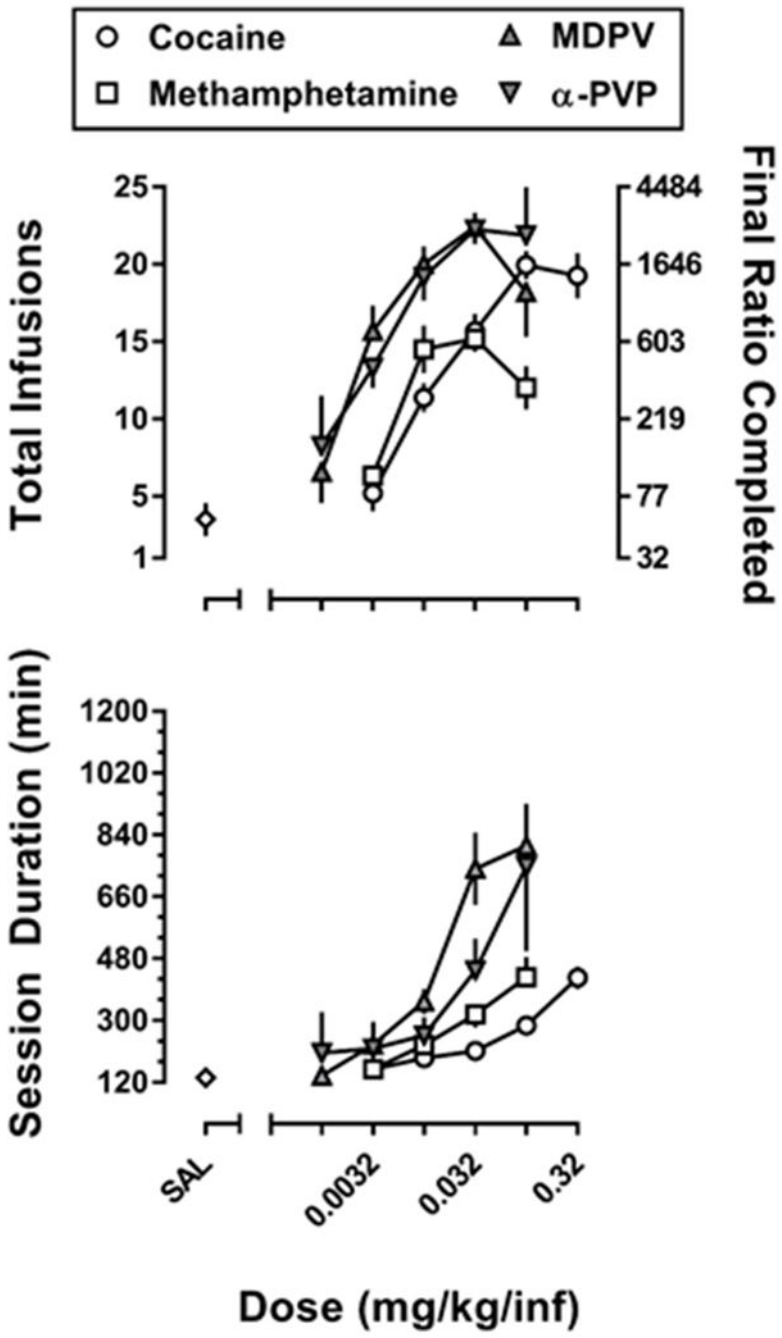

Figure 1.

Dose-response curves for the self-administration of cocaine, methamphetamine, MDPV, and α-PVP in rhesus monkeys (n=4) responding under a progressive ratio (PR) schedule of reinforcement. Top Panel: Data represent the mean (± 1 SEM) for the total number of infusions earned for cocaine (0.0032-0.32 mg/kg/inf), methamphetamine (0.0032-0.1 mg/kg/inf), MDPV (0.001-0.1 mg/kg/inf) and α-PVP (0.001-0.1 mg/kg/inf; left ordinate), as well as the corresponding final ratio completed (right ordinate). Bottom Panel: Data represent the mean (± 1 SEM) for the session duration in minutes for each dose of each drug.

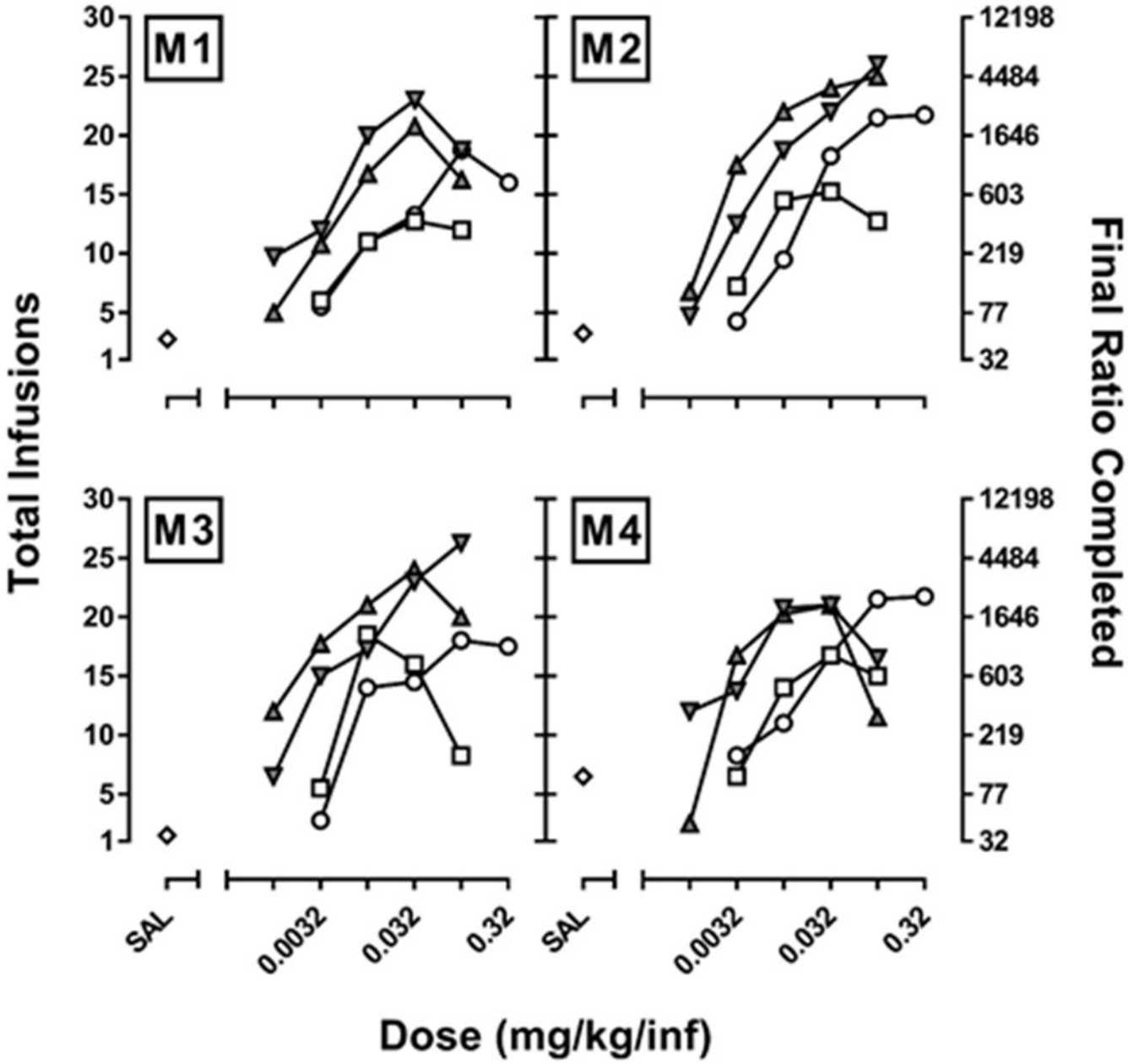

Figure 2.

Dose-response curves for the self-administration of cocaine, methamphetamine, MDPV, and α-PVP in each of 4 rhesus monkeys (M1-M4) responding under a progressive ratio (PR) schedule of reinforcement. Data represent the mean (± 1 SEM) for the total number of infusions earned for cocaine (0.0032-0.32 mg/kg/inf), methamphetamine (0.0032-0.1 mg/kg/inf), MDPV (0.001-0.1 mg/kg/inf) and α-PVP (0.001-0.1 mg/kg/inf; left ordinate), as well as the corresponding final ratio completed (right ordinate).

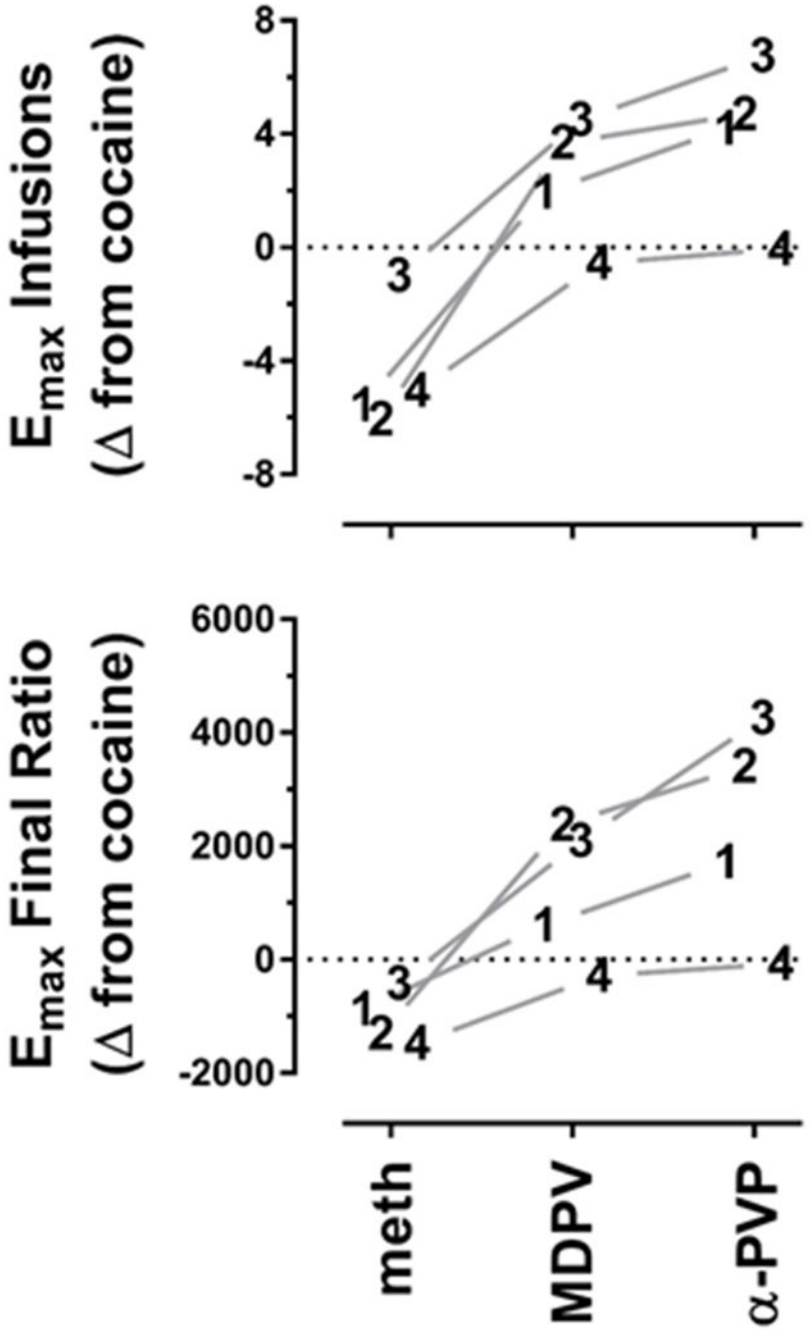

Figure 3.

Estimates of reinforcing effectiveness obtained for methamphetamine, MDPV, and α-PVP, normalized to cocaine for each of 4 rhesus monkeys (identified as 1, 2, 3, or 4). Top Panel: Data represent the maximum number of infusions of methamphetamine, MDPV, and α-PVP earned, normalized to the maximum number of infusions earned for cocaine for each monkey. Bottom Panel: Data represent the final ratio completed for the dose that maintained

the maximum number of infusions of methamphetamine, MDPV, and α-PVP earned, normalized to the final ratio completed for cocaine for each monkey.

Table 1.

Relative reinforcing effects of cocaine, methamphetamine, MDPV, and α-PVP in rhesus monkeys.

	ED_{50} mg/kg/inf (95% CI)	E_{max}		Max Duration min (SEM)
		Infusions (SEM)	Final Ratio (SEM)	
cocaine[a]	0.012 (0.01-0.014)	20.1 (1.0)[#]	1936 (270)	436 (28)
cocaine[b]	0.011 (0.007-0.017)	20.7 (0.6)[#]	2133 (229)	483 (40)
methamphetamine	0.0045 (0.0033-0.0062)	15.9 (1.1)	913 (168)	447 (39)
MDPV	0.0025 (0.0016-0.0040)	22.8 (1.0)[#]	3133 (668)[#]	841 (131)[*,#]
α-PVP	0.0029 (0.0016-0.0052)	24.3 (1.1)[*,#]	4260 (917)[*,#]	755[#] (121)

[a] initial evaluation of cocaine;

[b] terminal evaluation of cocaine

[*] significant difference from cocaine as determined by one-way ANOVA with post-hoc Tukey's tests;

[#] significant difference from methamphetamine as determined by one-way ANOVA with post-hoc Tukey's tests