

# Reinforcing effects of smoked methamphetamine in rhesus monkeys

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## Abstract

**Rationale** The occurrence of methamphetamine (METH) use by the smoking route is increasing. A nonhuman primate model for examining the reinforcing effects of smoked METH would be valuable for testing potential interventions for treating METH abuse disorders.

**Objective** The purpose of the present study was to examine the reinforcing effects of smoked METH in monkeys.

**Materials and methods** Four rhesus monkeys were trained to smoke cocaine (COC) under a chain fixed-ratio (FR) 64 lever press, FR 5 inhalation schedule of reinforcement. Upon observing stable levels of self-administration, METH was substituted for COC and a dose-response function for METH (0.08–0.8 mg/kg) was determined. Subsequently, the number of deliveries of COC (1 mg/kg), and 0.2 and 0.8 mg/kg METH were examined across increasing response requirements.

**Results** METH was dose-dependently self-administered. Higher doses of METH (0.2, 0.4, and 0.8 mg/kg) produced asymptotic levels of responding that were slightly lower than those obtained with 1 mg/kg COC. Numbers of deliveries of COC and METH decreased as response requirement increased. METH, however, maintained fewer deliveries than 1 mg/kg COC at most response requirements.

**Conclusions** METH is readily self-administered by smoking in rhesus monkeys when substituted for COC. METH may have a lower reinforcing strength than COC, but further research is needed to fully characterize its relative reinforcing strength.

**Keywords** Methamphetamine · Cocaine · Rhesus monkey · Smoking · Relative persistence · Self-administration

## Introduction

Stimulant abuse is on the rise within the United States population and, excluding cocaine, METH is the most frequently used illicit stimulant (SAMHSA 2005a). The National Survey on Drug Use and Health Report (2003) indicated that 12.3 million people aged 12 or older abused METH at least once in their lifetime (SAMHSA 2005a). METH can be administered by various routes, a factor that likely contributes to its popularity for abuse. An increasing trend toward smoking METH has been observed. For example, in 1992 only 12% of the METH-abusing population smoked METH; more recently, however, smoking has become the preferred route of administration with 50% of users smoking METH in 2002 (SAMHSA 2005b). When smoked, METH produces rapid onset of effects characterized by a “rush” similar to the effect achieved when it is injected intravenously. In an earlier study, Cook et al. (1993) reported that in human subjects, smoked METH produced subjective and cardiovascular effects similar to an intravenous injection of METH. They demonstrated that the peak for METH’s subjective effects was reached about 18 min after both smoked and intravenous administrations, and the peak change in heart rate was observed at about 12 min after administration for both routes (Cook et al. 1993).

The reinforcing effects of METH have been demonstrated in several species. METH is self-administered intravenously by rats (Roth and Carroll 2004; Yokel and Pickens 1973), nonhuman primates (Balster and Schuster 1973a; Woolverton et al. 1984), cats (Balster et al. 1976), and

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humans in a laboratory setting (Hart et al. 2001). METH engenders discriminative stimulus effects that generalize to other psychostimulants including methylphenidate and COC in squirrel monkeys (Czoty et al. 2004). Compared to other drugs of abuse, such as COC, METH's relative reinforcing strength is unknown.

Currently, there are no reports evaluating the reinforcing effectiveness of METH via the inhalation route in laboratory animals. Previous work has demonstrated that COC, heroin, and combinations thereof ("speedball") are reliably self-administered by smoking in rhesus monkeys (Carroll et al. 1990; Mattox and Carroll 1996; Mattox et al. 1997). One purpose of the current study was to characterize the dose–response relationship of smoked METH in monkeys. A smoking model of METH self-administration in the monkey will contribute important information regarding its reinforcing effectiveness, and it will establish a method for emulating the most common route of administration of METH among users. The second purpose of this experiment was to compare the reinforcing strength of doses of METH that maintained greatest delivery numbers to a dose of COC that has previously been shown to maintain maximal numbers of deliveries (Carroll et al. 1990). To this end, 1 mg/kg COC and two doses of METH, 0.2 and 0.8 mg/kg, were tested under increasing response requirements. Differences in reinforcing strength between 1 mg/kg COC and 0.2 and 0.8 mg/kg METH were also evaluated by comparing relative persistence ratios as described by Meisch (2000). It was predicted that METH would be self-administered by smoking in a dose-dependent manner and that self-administration would decrease with increases in response requirements.

## Materials and methods

### Subjects

Five adult male rhesus macaque monkeys (*Macaca mulatta*, 8.9–12.2 kg) served as experimental subjects. All subjects had extensive histories of self-administering drugs (cocaine, heroin) via the inhalation route (mean: 172.6 months; range: 129–213 months). For the present studies, they had most recently been maintained on a cocaine smoking baseline. Monkeys were maintained at 85% of their free-feeding weights, and they were fed measured allotments of monkey chow (Teklad; Bartonville, IL, USA) and fresh fruit and/or trail mix after their daily experimental sessions. Monkeys were examined several times each week by veterinary staff. They were weighed monthly and, if needed, food allotments were adjusted to maintain their 85% free-feeding weights. They were individually housed in a temperature- and humidity-controlled colony room on a

12-h light/dark schedule with lights on at 0600 hours. All procedures and protocols were approved by the University of Minnesota Institutional Animal Care and Use Committee. Laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). Laboratory practices were consistent with the "Guide for the Care and Use of Laboratory Animals" (National Research Council, 2003).

### Apparatus

Monkeys were housed in individual, custom-made stainless steel cages (83 cm in width × 76 cm in height × 100 cm in depth; Lab Products, Maywood, NJ, USA) consisting of solid back and side walls, a barred front door, grid floors, and a primate perch. One of the side walls was modified to accommodate an intelligence panel with two brass spouts (1.2 cm in diameter) that extended 2.7 cm into the cage through circular cutouts in the wall about 45 cm above the cage floor. There were three stimulus lamps placed equidistantly on the panel. Two green-colored lamps were located above the spouts, and one red-colored lamp was located centrally above a response lever. The green stimulus lamps signaled the availability of deliveries of water (left spout) or smoke (right spout) upon activation; the red stimulus lamp above the response lever signaled trial onset, and it remained on until the lever-press FR was completed. The left spout was used for drinking, and 0.60 ml of water was delivered upon each lip-contact response. The spout located on the right was used for smoke deliveries. Each spout was mounted on clear Plexiglas with embedded green and white stimulus lamps that were illuminated when water (left) or smoke (right) was being delivered. Scheduling and recording of events were accomplished using Med-PC software (Med-PC® for Windows) and associated interfaces (Med Associates, St Albans, VT, USA) located in an adjacent room.

The smoking device has been described in detail previously (Carroll et al. 1990). Briefly, it consisted of a coil unit that could be inserted directly into the back of the smoking spout from outside the cage and behind the intelligence panel. The coil was comprised of a nichrome wire mounted on a machined plastic Delrin® (DuPont, Wilmington, DE, USA) plug customized to fit into the spout. The plug was embedded with two brass connectors attaching the nichrome coil on one end, and on the other end wires connected to a two-pronged connector that plugged into an electrical unit that supplied power for heating the coil. Limits on the heating unit were imposed to prevent the pyrolysis of the drug material. The smoking spout was equipped with a solenoid device that allowed a mixture of air with smoke during inhalation. Upon completing the response requirement for inhalation

responses (FR 5), a vacuum sensor was activated that signaled the onset of the heating mechanism. Each coil contained one unit dose of the drug, and after the monkey smoked a coil, the experimenter replaced the used coil with another coil containing a full dose of drug to be used in the next trial. Measured amounts of METH or COC dissolved in 95% ethanol were applied to the nichrome coil using a 1-ml syringe. The coils were allowed to dry for at least 24 h at room temperature before use to ensure that the ethanol fully evaporated leaving the drug deposited on the coil.

Water was available from the drinking spout (left), and it was delivered upon each lip contact (FR 1) that closed an electronic drinking circuit. This, in turn, activated a solenoid-operated valve permitting approximately 0.60 ml of water to flow from reservoirs suspended above the operant panel. Monkeys were allowed to drink water from their left-side spout during the experimental session (0830–1230 hours) and during the intersession period (1250–0730 hours).

## Drugs

Cocaine base and D-methamphetamine HCl were obtained from the National Institute on Drug Abuse (Research Triangle Park, NC) and were dissolved in 95% ethanol, which was obtained from the University of Minnesota Chemical Storehouse.

## Schedule of reinforcement

Monkeys were maintained under a chain FR 64 lever press, FR 5 inhalation schedule of reinforcement. Upon the beginning of the daily experimental sessions, the green stimulus lamp located above the water spout and the red center stimulus lamp above the response lever were illuminated to signal the onset of a trial. Completion of the lever-press response requirement was signaled by the flashing of the green stimulus lamp (10 Hz) above the smoking spout that indicated the availability of a smoke delivery contingent upon five inhalation responses. The fifth inhalation response initiated the heating of the drug coil and subsequent vaporization of drug. Each delivery was followed by a 15-min timeout (TO) period, during which the stimulus lights in the center of the panel and above the smoking spout were extinguished and lever pressing and inhalation responses were without scheduled consequences. At the end of the TO, the next trial was signaled by the onset of the red center stimulus lamp. A maximum of ten trials were allowed during the daily experimental session. Each trial was 30-min in duration. If a monkey failed to complete the lever press and inhalation response contingencies during the 30 min, the trial was aborted and the next trial was begun.

## Dose and fixed ratio substitutions

Before testing METH, monkeys were trained to smoke COC base (1 mg/kg/delivery). When monkeys reliably self-administered all ten of the available COC deliveries for three consecutive days, doses of METH (0.08, 0.12, 0.2, 0.4, and 0.8 mg/kg/delivery) were substituted in a nonsystematic order without returning to COC baselines in between METH dose changes. Each dose was self-administered for at least three sessions or until smoking behavior was stable to minimize carryover effects from one drug condition to the next, and the sequence of METH dose substitutions differed across monkeys. Stability of behavior was defined as no steadily increasing or decreasing trends in delivery numbers for three consecutive sessions, such that both highest and lowest numbers of deliveries did not occur on the first and last sessions (or vice versa) and the range of delivery numbers did not deviate by more than two deliveries for three consecutive days. The METH dose–response function was obtained under a chain FR 64 lever press FR 5 inhalation response schedule of reinforcement. A FR 64 schedule for lever pressing was chosen because a lower response requirement may not have been as sensitive for detecting a difference dose, and it was the highest FR at which all monkeys would reliably self-administer METH by smoking.

After stable self-administration was observed, numbers of deliveries of 1 mg/kg COC, and 0.2 and 0.8 mg/kg METH were examined. Reinforcing strength for 1 mg/kg COC and each dose of METH was examined as a function of response requirement. The FR values (i.e., 64, 128, 256, 512, and 1,024) were evaluated in a nonsystematic order across monkeys. The inhalation response requirement was maintained at FR 5 throughout the study. Monkeys self-administered each dose under each FR condition until there were no steadily increasing or decreasing trends in delivery numbers for three consecutive sessions as described above. Doses of 0.2 and 0.8 mg/kg METH were chosen for this analysis to further characterize their reinforcing effects. Additionally, because both doses maintained similar numbers of smoke deliveries, they were tested under conditions of increasing response requirements to determine potential differences in their reinforcing strengths. For the present studies, reinforcing strength is defined as the level of lever pressing maintained by a drug condition across increasing response requirements. The dose of cocaine used (1 mg/kg) was chosen as it was previously shown to maintain maximal numbers of deliveries (Carroll et al. 1990). Upon completion of the METH dose–response and analyses of reinforcing strength, monkeys were returned to their COC baselines, and they self-administered 1 mg/kg COC under the chain FR 64 FR 5 schedule.

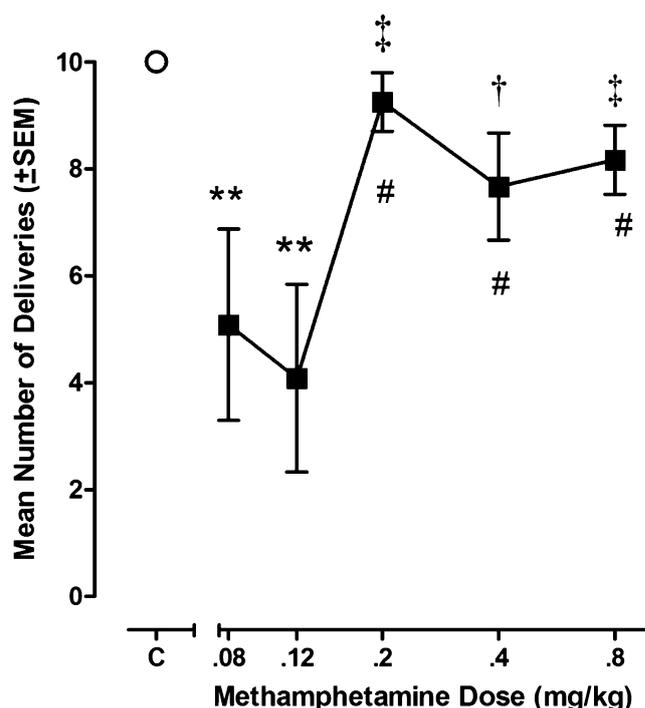
## Data analysis

Mean numbers of smoke deliveries and responses maintained by doses of METH and COC taken from three consecutive days of stable behavior for each monkey were used for analyses. The individual means were averaged across monkeys. A one-way repeated measures analysis of variance (ANOVA) was conducted on the number of smoke deliveries as the dependent measure for the independent variable of drug condition (1 mg/kg COC and 0.08, 0.12, 0.2, 0.4, and 0.8 mg/kg METH). A Bonferroni post-hoc test corrected for multiple comparisons was conducted after the detection of overall significant effects ( $P < 0.05$ ). To examine the effect of altering response requirement on numbers of deliveries, a two-way repeated measures ANOVA was conducted on drug condition (0.2 and 0.8 mg/kg METH and 1 mg/kg COC) and response requirement (FRs 64, 128, 256, 512, and 1024). Bonferroni post-hoc tests corrected for multiple comparisons were conducted when overall ANOVAs revealed significant differences ( $P < 0.05$ ). All lever-press responses (except those emitted during timeout) were analyzed using a separate two-way repeated measures ANOVA; however, the response data violated the assumption for homogeneity of variance, therefore a Games–Howell post-hoc test was used to correct for heterogeneity when an overall significance was detected.

As a measure of relative reinforcing strength, relative persistence as described by Meisch (2000) were calculated by dividing the number of deliveries obtained at higher response requirements (FRs 128, 256, 512, and 1,024) by the number of deliveries obtained at the lowest response requirement (FR 64) and multiplied by 100 to derive a percentage. For analyses of relative persistence, the percent data were subjected to a log transformation and a two-way repeated measures ANOVA was conducted on the transformed values. A Bonferroni post-hoc test corrected for multiple comparisons was conducted after the detection of overall significant effects ( $P < 0.05$ ).

## Results

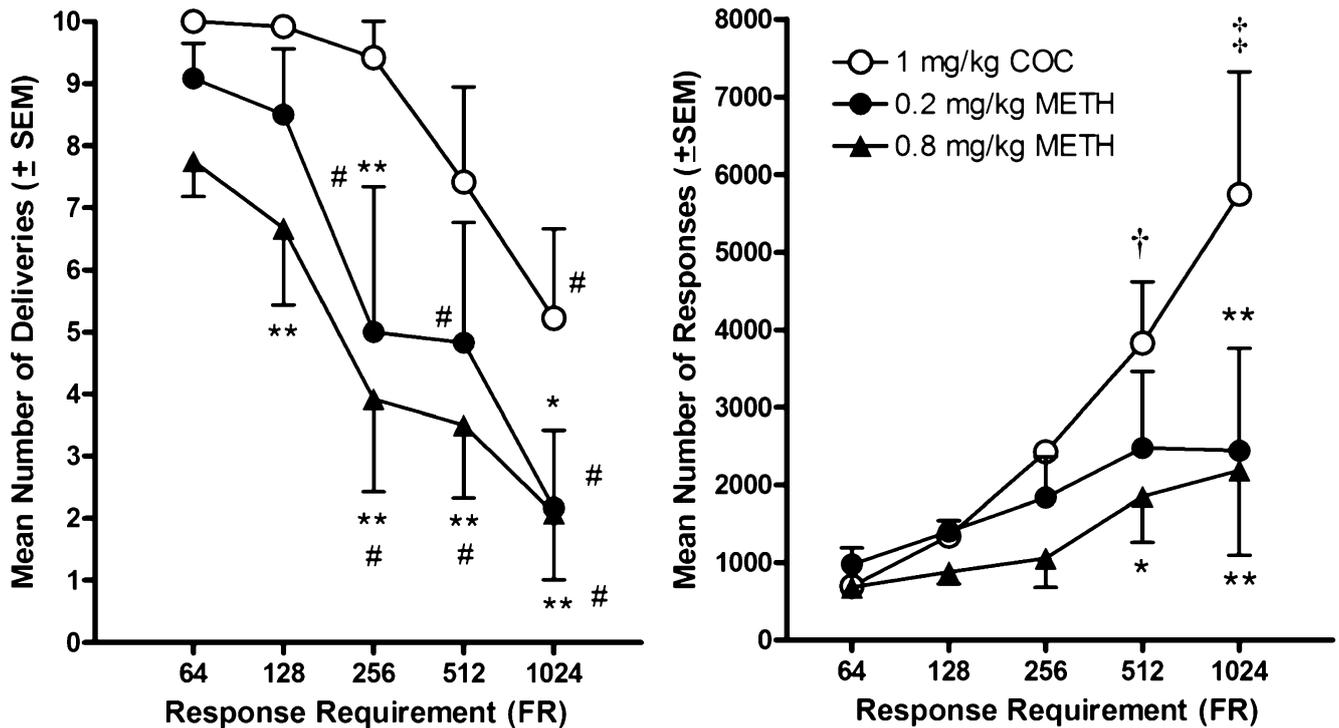
Four of the five monkeys readily self-administered all doses of METH when it was substituted for COC. One monkey (M-S) self-administered METH at 0.8 mg/kg/delivery but ceased smoking when other doses were substituted; therefore, his data were excluded from analyses. Figure 1 shows the mean number of deliveries of COC and five doses of smoked METH for the group of four monkeys. As expected, COC (1 mg/kg) maintained the greatest number of smoke deliveries, which was a maximum of 10. A significant effect for drug condition (i.e., COC or METH dose) was found [ $F(5, 71) = 16.15$ ,  $P < 0.0001$ ]. Bonferroni-



**Fig. 1** Mean ( $\pm$ SEM) numbers of METH (filled squares) and COC (unfilled circle) smoke deliveries as a function of METH dose or 1 mg/kg COC for the group of four monkeys. \*\* $P < 0.01$  compared to COC; † $P < 0.05$  compared to 0.08 mg/kg; ‡ $P < 0.01$  compared to 0.08 mg/kg; # $P < 0.01$  compared to 0.12 mg/kg

corrected post-hoc tests revealed significant differences in deliveries obtained at the 0.08 and 0.12 mg/kg doses compared to COC ( $P < 0.01$  for both doses). Post-hoc comparisons between doses of METH revealed that the number of deliveries obtained with 0.08 mg/kg METH was significantly different from those obtained at 0.2 mg/kg METH ( $P < 0.01$ ), 0.4 mg/kg METH ( $P < 0.05$ ), and 0.8 mg/kg METH ( $P < 0.01$ ). Also, statistically significant differences were found upon comparing 0.12 mg/kg METH to 0.2 mg/kg METH ( $P < 0.01$ ), 0.4 mg/kg METH ( $P < 0.01$ ), and 0.8 mg/kg METH ( $P < 0.01$ ).

The left panel of Fig. 2 shows the mean numbers of COC (1 mg/kg), 0.2 and 0.8 mg/kg METH deliveries as a function of response requirement for the group of four monkeys. Generally, numbers of smoke deliveries decreased as the response requirement increased for COC and both doses of METH. A two-way ANOVA revealed significant differences for drug condition [ $F(2, 179) = 13.95$ ,  $P < 0.0001$ ] and response requirement [ $F(4, 179) = 58.81$ ,  $P < 0.0001$ ]. A significant interaction between drug condition and response requirement was also detected [ $F(8, 179) = 2.23$ ,  $P < 0.05$ ]. Post-hoc comparisons revealed significant differences between COC and 0.2 mg/kg METH at FR 256 ( $P < 0.01$ ) and FR 1024 ( $P < 0.05$ ). Significant differences



**Fig. 2** (Left panel): mean ( $\pm$ SEM) numbers of 0.2 mg/kg METH (filled circles) and 0.8 mg/kg METH (filled triangles) and COC (unfilled circles) smoke deliveries as a function of response requirement (FR) for the group of four monkeys. \* $P$ <0.05 compared to COC; \*\* $P$ <0.01 compared to COC; # $P$ <0.01 compared to FR 64

within each drug condition. (Right panel): mean ( $\pm$ SEM) numbers of responses maintained by deliveries of 0.2 mg/kg METH (filled circles), 0.8 mg/kg METH (filled triangles) and COC (unfilled circles) as a function of FR. \*\* $P$ <0.01 compared to COC; † $P$ <0.05, ‡ $P$ <0.01 compared to COC FR 64

were also found between COC and 0.8 mg/kg METH at FR 128 ( $P$ <0.01), FR 256 ( $P$ <0.01), FR 512 ( $P$ <0.01), and FR 1,024 ( $P$ <0.01). No statistically significant differences were found between the two doses of METH. Examination of the effects of response requirement within each drug condition revealed significant differences. For 0.2 mg/kg METH, significant decreases were found when the FR value was increased from FR 64 to FR 256 ( $P$ <0.01), FR 512 ( $P$ <0.01), and FR 1,024 ( $P$ <0.01). For 0.8 mg/kg METH, significant differences were found when the FR value was increased from FR 64 to FR 256 ( $P$ <0.01), FR 512 ( $P$ <0.01), and FR 1,024 ( $P$ <0.01). For COC, a significant difference was found between FR 64 and FR 1,024 ( $P$ <0.01).

The right panel of Fig. 2 shows the mean numbers of responses as a function of response requirement. The numbers of responses maintained by COC increased monotonically with increases in response requirement. Both doses of METH, however, maintained fewer responses than COC as the requirement increased. A two-way ANOVA conducted on responses revealed a significant main effect for drug condition [ $F(2, 179)=9.66, P$ <0.01]. Games–Howell post-hoc tests revealed significant differences between COC and 0.2 mg/kg METH at FR 1,024 ( $P$ <0.01), as well as COC and 0.8 mg/kg METH at FR

512 ( $P$ <0.05) and at FR 1,024 ( $P$ <0.01). A significant main effect was also observed for response requirement [ $F(4, 179)=35.73, P$ <0.01]. Post-hoc tests indicated significant differences for COC between FR 64 and FR 512 ( $P$ <0.05) and between FR 64 and FR 1,024 ( $P$ <0.01).

Relative persistence of lever pressing responding maintained by COC, and 0.2 and 0.8 mg/kg METH is shown in Table 1. Increasing the response requirements produced

**Table 1** Mean relative persistence of responding maintained by deliveries of COC and METH obtained at FRs 128, 256, 512, and 1,024 expressed as a percentage of the number of deliveries obtained at FR 64

Relative persistence				
Drug condition	FR 128/FR 64 (%)	FR 256/FR 64 (%)	FR 512/FR 64 (%)	FR 1024/FR 64 (%)
1 mg/kg COC	99.17	94.17	74.17	52.22
0.2 mg/kg METH	92.83	51.64	50.30	21.67*
0.8 mg/kg METH	88.20	56.30	48.97	31.00

\* $P$ <0.05 compared to COC

decreases in persistence of responding maintained by COC and both doses of METH. A significant difference was found for response requirement [ $F(3, 47)=11.19, P<0.01$ ]. Specifically, responding maintained by COC was more persistent than that maintained by 0.2 mg/kg METH at FR 1,024 ( $P<0.05$ ). The relative persistence of responding maintained by 0.2 and 0.8 mg/kg METH was comparable across response requirements.

## Discussion

The results of the present study indicate that METH self-administration via inhalation was reliably maintained in a dose-dependent manner in rhesus monkeys trained to smoke COC. Other drugs of abuse that are smoked by humans, such as COC and heroin (Carroll et al. 1990; Evans et al. 2003; Mattox and Carroll 1996), as well as combinations thereof (Mattox et al. 1997), are also smoked by rhesus monkeys. The findings of the present study extend our previous research with smoked drugs of abuse to include METH. Demonstration of METH self-administration via smoking by monkeys is important, as smoking is increasingly reported as the preferred route of self-administration in humans (SAMHSA 2005b). Furthermore, the smoking model of drug abuse is representative of human drug abuse behavior. For example, patterns of COC intake are similar in humans (Hatsukami et al. 1994) and rhesus monkeys (Carroll et al. 1990). Importantly, behavioral and pharmacological treatments used in the smoking model have similar outcomes to those reported in humans (Carroll et al. 2001). This is also well documented for combined pharmacological and behavioral treatments. For example, in monkeys, behavior maintained by smoked COC is affected by treatment with buprenorphine to a greater degree when alternative reinforcers are available (Rodefer et al. 1997). A similar reduction in behavior is observed in nicotine-dependent humans when a non-drug incentive is paired with free cigarette puffs (a simulated medication) (Bickel et al. 1997).

In the present study, the dose–response analysis for METH resulted in a function in which the numbers of smoke deliveries remained elevated instead of decreasing. Thus, the curve was asymptotic unlike the typical inverted U-shaped curve observed with intravenous METH in rhesus monkeys (Balster and Schuster 1973a). Previous studies conducted in this laboratory have shown that COC (Carroll et al. 1990) and heroin (Mattox and Carroll 1996) produce dose–response curves that are similar in shape to the dose–response curve obtained with METH in the present study. Furthermore, studies involving COC smoking in humans have demonstrated asymptotic dose–response curves (Hatsukami et al. 1994). One other laboratory using the

smoking procedure in monkeys also demonstrated the absence of a descending limb when a dose–response function was determined with heroin (Foltin and Evans 2001). The lack of a descending limb in the dose–response curves may be attributable to the experimental parameters of the smoking procedure, such that a limited number of trials precluded the possibility of greater increases at intermediate doses. Additionally, a decrease in the number of METH deliveries might have been observed if higher doses had been tested.

The doses of METH used in the present study were chosen to be comparable to those used in intravenous self-administration studies in monkeys (Balster and Schuster 1973a; Woolverton et al. 1984) and smoked METH in humans (Perez-Reyes et al. 1991). Under the conditions of the present study, METH and COC were self-administered under identical experimental parameters, but extending the length of the trials or the duration of the intertrial timeout may have resulted in greater numbers of METH deliveries at higher response requirements. Another possible interpretation is that monkeys titrated their intake by regulating the volume of smoke inhaled. A previous study conducted in this laboratory (Carroll et al. 1990) demonstrated that COC blood levels and physiological effects are comparable to those in humans when a similar laboratory model was used (Hatsukami et al. 1990). Furthermore, remote observations indicated that monkeys were maintaining full contact with the smoking spout for the duration of the period that the smoke was being produced, suggesting the monkeys were receiving the full dose available.

In the analysis of reinforcing strength, a significant interaction between response requirement and drug condition was found, indicating that differences between COC and METH varied across response requirements in a nonparallel manner. Numbers of 0.8 mg/kg METH deliveries obtained at higher FR values were fewer than those for COC, suggesting that this dose of METH had a lower reinforcing strength. Previous work has also shown that smoked COC self-administration is more resistant to behavioral (Comer et al. 1994; Cosgrove and Carroll 2002) and pharmacological (Cosgrove and Carroll 2002) treatment interventions at low- vs high-response requirements. Additionally, analyses of relative persistence, which involve comparisons of behavior maintained at the lowest FR with that maintained at each of the higher FRs, indicate that behavior maintained by 1 mg/kg COC was more resistant to increasing response requirements than either dose of METH. This suggests that the reinforcing effectiveness of 1 mg/kg COC was greater than either dose of METH, particularly at higher response requirements.

Reinforcers of greater magnitude typically maintain greater relative persistence (Meisch 2000), therefore, it was predicted that 0.8 mg/kg METH would maintain a

greater relative persistence than the lower dose of 0.2 mg/kg. However, in the present study, the values of relative persistence of lever-pressing behavior maintained by the two doses of METH were similar. The lack of a difference in the number of deliveries obtained for 0.2 and 0.8 mg/kg METH could be attributable to the route of administration. As discussed above, the smoking route of administration does not produce an inverted U-shaped curve that is normally seen using the intravenous route of administration. These results suggest that higher doses of METH are not necessarily of greater reinforcing value under the conditions of the present study.

The observed difference in reinforcing strength between doses of COC and METH that maintain maximal levels of behavior may be attributable to the differences in the onset of action and duration related to their reinforcing effects. Subjective effects produced by COC and METH have been shown to differ temporally in humans. METH produces a slower onset of subject-rated effects that have a slower onset and remain elevated for a longer period of time relative to COC, which produces rapid peak levels of subjective effects that dissipate earlier. For example, for subject ratings of “high” and “stimulated”, METH produces peak ratings 10–15 min later than COC and the subject-rated effects produced by METH persisted for at least 20–30 min longer (Newton et al. 2005). Czoty et al. (2004) found that in squirrel monkeys, COC and METH produced similar increases in extracellular dopamine; however, the peak increase induced by METH manifested about 10 min later than the peak increase by COC. Given the slightly slower onset of dopamine increase in squirrel monkeys and slower prevalence of subjective effects after METH administration in humans, one might speculate that onset and duration of action of METH relative to COC are slower and longer, respectively. Such temporal differences may influence reinforcing stimulus effects of drugs.

It is well known that altering the onset of a drug's effects by imposing a delay (Beardsley and Balster 1993) or by increasing the duration with which the infusion is delivered (Balster and Schuster 1973b) can decrease a drug's reinforcing effects. Woolverton and Wang (2004) demonstrated that lengthening the duration of the infusion of COC from 10 to 600 s reduced its reinforcing strength, although the longer duration infusion still maintained self-administration. Recent evidence in humans has shown that rate of infusion, as well as dose, alters the subject-rated effects of COC (Nelson et al. 2006). Winger et al. (2002) demonstrated that NMDA receptor antagonists with faster onset for producing observable behavioral effects also had greater reinforcing strength compared with drugs having a slower onset, suggesting that reinforcing strength is related to the onset of action. Lower reinforcing effectiveness has also been demonstrated with dopamine transporter-preferring

compounds that demonstrate slower binding kinetics (Wee et al. 2006). While the longer duration of action of METH may account for some differences described in the present study, there is evidence suggesting that duration of action is not as important as onset of action in determining reinforcing strength (Lile et al. 2003; Panlilio and Schindler 2000; Woolverton et al. 2002). Findings from the present study suggest that 1 mg/kg COC has greater reinforcing strength than 0.2 and 0.8 mg/kg METH. However, further evaluation with additional doses of COC is necessary to compare its reinforcing strength with that of METH.

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