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The Relative Reinforcing Strength of Methamphetamine and *d*-Amphetamine in Monkeys Self-Administering Cocaine

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Abstract

Epidemiological data indicate that rates of methamphetamine misuse surpass those of *d*-amphetamine, but self-administration research in animals and humans has not typically demonstrated differences in their reinforcing effects. The present study used a within-session, exponentially-increasing progressive-ratio schedule and extended-access conditions to assess the relative reinforcing strength of *d*-amphetamine and methamphetamine in rhesus monkeys ($n=5$) trained to self-administer cocaine. A range of doses of methamphetamine (0.003–0.1 mg/kg/injection), *d*-amphetamine (0.003–0.1 mg/kg/injection) and cocaine (0.003–0.3 mg/kg/injection) was tested to capture the ascending and descending limbs of the dose-effect functions. Each drug functioned as a reinforcer, but the peak number of self-administered *d*-amphetamine injections was significantly lower compared to methamphetamine and cocaine; the peak number of self-administered injections of cocaine and methamphetamine did not differ. Although differences in availability and other social factors likely impact relative rates of abuse, the present data suggest that the greater reinforcing strength of methamphetamine contributes to its increased use compared to *d*-amphetamine.

Keywords

Cocaine; amphetamine; drug abuse; abuse liability; abuse potential; reinforcing strength; rhesus monkey

INTRODUCTION

Epidemiological data indicate that methamphetamine misuse in the United States surpasses *d*-amphetamine abuse. More specifically, self-reported use, emergency department (ED) visits and treatment admission rates are greater for methamphetamine compared to *d*-amphetamine (SAMHSA, 2011; 2012a,b). The reinforcing effects of a drug are a defining characteristic of its abuse potential, and results from self-administration procedures should reflect the prevalence of misuse. Contrary to this prediction, self-administration studies in animals and humans have not typically demonstrated differences in the reinforcing effects of methamphetamine and *d*-amphetamine (Balster and Schuster, 1973; Deneau et al., 1969; Johanson et al., 1976; Kirkpatrick et al., 2012; Yokel and Pickens, 1973). Although a variety

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of societal factors likely influence relative use rates (e.g., greater access to methamphetamine due its ease of synthesis), another possible explanation for this discrepancy is that the self-administration conditions used previously were not sensitive to the relative reinforcing strength of *d*-amphetamine and methamphetamine. The present study, used a within-session, exponentially-increasing progressive-ratio (PR) schedule, extended-access conditions across a wide range of doses that captured the ascending and descending limbs of the dose-effect functions, in an effort to maximize the ability to detect differences in the relative reinforcing strength of these amphetamines.

METHODS

Subjects

Five adult male rhesus monkeys (*Macaca mulatta*), having similar previous histories with cocaine and other monoamine transporter ligands (Lile et al., 2002, 2003) served as subjects. Each animal was surgically implanted under sterile conditions with a chronic indwelling, single-lumen catheter (see Lile et al. 2002 for details). Monkeys were maintained at 95% of free-feeding body weight. Procedures were conducted in accordance with guidelines provided by the NIH Office of Protection from Research Risks. The protocol for this experiment was reviewed and approved by the Wake Forest University Animal Care and Use Committee.

Apparatus

Monkeys were individually housed in sound-attenuating cubicles (91 cm³; Plas Labs, Lansing, MI) within an environmentally-controlled room. Cubicles included a Plexiglas front wall equipped with two response levers (BRS/LVE, Beltsville, MD) and stimulus lights, as well as peristaltic infusion pumps (Cole-Parmer Co., Chicago, IL). Each animal was fitted with a stainless-steel restraint harness and spring arm (Restorations Unlimited, Chicago, IL) attached to the cubicle.

Procedure

Experimental sessions were typically conducted 7 days/week. Daily activities were scheduled to permit a maximum 20-h session length. At 10.00 h, catheters were flushed with heparinized saline (100 U/ml) and the animals were fed; at 14.00 h catheters were filled with the solution available for self-administration and the session was initiated.

Monkeys responded under a within-session, exponentially-increasing PR schedule (Richardson and Roberts, 1996: $\text{ratio} = 5 * \text{exponent}(S^R \# * 0.2) - 5$). The first ratio requirement was 50 responses, corresponding to the 12th value of the equation (Table 1). A 10-min time out followed each injection. The breaking point (BP) was defined as the final ratio completed when 2 h had elapsed without an injection delivered. In all cases, the BP was reached within the 20-h session limit.

When responding maintained by the baseline cocaine dose (0.03 or 0.1 mg/kg/injection) was stable ($\pm 20\%$ of the mean number of injections for three consecutive sessions, with no trends), saline was substituted for at least 5 sessions and until the number of injections stabilized at less than 20% of the cocaine baseline. Following a return to the cocaine baseline, doses of cocaine (0.003–0.3 mg/kg/injection; $n=5$), *d*-amphetamine (0.003–0.1 mg/kg/injection; $n=4$) and methamphetamine (0.003–0.1 mg/kg/injection; $n=4$) were made available for self-administration; doses of each drug were tested in mixed order. Test doses were available for at least 5 consecutive sessions with a return to the cocaine baseline for at least 3 sessions between doses.

Statistical Analysis

Data are the means from the last three sessions in which each drug was available. Baseline cocaine data represent an average of the three sessions preceding test dose determinations. Data for each drug were fit to individual linear mixed models (SAS Institute Inc., v9.3, Cary, NC), expressing the mean number of injections as a function of dose. Models also included a subject-specific random effect to account for correlations among multiple measurements from the same monkeys. Results were judged by a Type III F test of fixed effects. Statistical significance was defined by $p \leq 0.05$. Post-hoc tests were used to compare saline to each dose. A similar analytical strategy tested for differences in the peak number of injections across drugs.

Drugs

(–)Cocaine was provided by the National Institute on Drug Abuse (Bethesda, MD). *d*-Amphetamine and *d*-methamphetamine were purchased from Sigma-Aldrich (St Louis, MO). Drug concentrations were calculated according to the salt form; all drugs were dissolved in sterile saline.

RESULTS

The mean number of self-administered injections of cocaine, *d*-amphetamine, methamphetamine and saline are shown in Figure 1. When saline was substituted for the training dose of cocaine, the number of injections dropped from 12.9 ± 2.2 (mean $\pm$ SD; corresponding to a BP of 637 ± 239 responses) to an average of $1.4 (\pm 0.37)$; corresponding to a BP of 55 ± 4.8 responses). Statistical analysis revealed a significant main effect of dose for cocaine ($F_{4,44}=28.9$; $p<0.001$), *d*-amphetamine ($F_{3,44}=5.37$; $p<0.005$) and methamphetamine ($F_{3,44}=20.2$; $p<0.001$). Post-hoc comparisons indicated that the number of self-administered injections for all but the lowest dose of each drug was significantly greater than for saline. Analysis of maximum self-administered injections revealed a significant main effect of drug ($F_{8,44}=8.8$; $p<0.001$). Post-hoc analysis demonstrated that the peak number of self-administered injections of cocaine (16.4 ± 3.5 , corresponding to a BP of 1467 ± 940 responses, at the 0.1 mg/kg/injection dose) and methamphetamine (17.2 ± 3.7 , corresponding to a BP of 1761 ± 843 responses, at the 0.03 mg/kg/injection dose) did not differ, but were significantly greater than for *d*-amphetamine (10.3 ± 4.2 , corresponding to a BP of 793 ± 526 responses, at the 0.03 mg/kg/injection dose).

DISCUSSION

Under the conditions of the present study, the relative reinforcing strength of methamphetamine was greater than that of *d*-amphetamine in rhesus monkeys. This outcome parallels epidemiological data showing greater incidence of abuse for methamphetamine compared to *d*-amphetamine (SAMHSA, 2011; 2012a,b). The mechanism underlying this difference is unknown, but it could be due to the presence of an *N*-methyl group on methamphetamine, which could translate to more rapid CNS penetration due to increased lipophilicity (Gulaboski et al., 2007) and consequently increased reinforcing effects (reviewed in Lile, 2006). Other differences, such as drug-specific regional dopamine and glutamate release as has been observed in rodents (e.g., Shoblock et al., 2003), might also have contributed to the divergence in their relative reinforcing strength

A PR schedule was chosen for this study because BPs provide an index of relative reinforcing strength, unlike ratio and other simple schedules that yield only response rate data (Woolverton and Nader, 1990; Banks and Negus, 2012), which limits the conclusions that could be drawn from the earlier studies comparing self-administration of these

amphetamines. Results from a study in humans (Kirkpatrick et al., 2012), using a concurrent PR, drug-money choice procedure were suggestive of equivalent reinforcing strength for methamphetamine and *d*-amphetamine self-administration. However, ethical and practical constraints of clinical research restrict the length of study participation and drug exposure, which could have limited the sensitivity to detect potential differences in reinforcing strength.

Extended-access conditions were used in an effort to limit the impact that duration of action and associated rate-decreasing effects might have on BP. Peak methamphetamine BPs did not differ from those of cocaine, despite apparent differences in their half-lives, but were significantly greater compared than those of *d*-amphetamine despite more similar durations of action ($t_{1/2}$ = 2.8 h for cocaine, 10.7 h for methamphetamine, 16 h for *d*-amphetamine; calculated in humans; Harris et al., 2003; Herbst et al., 2011). These results are consistent with previous studies suggesting that reinforcing strength is not a function of duration of action (reviewed in Lile, 2006). The present results are also consistent with an older study (Yanagita, 1973) in monkeys that used a PR schedule, 24-h drug availability and single doses (albeit comparable to those that maintained peak responding here), and similarly found higher BPs for methamphetamine than *d*-amphetamine, though direct comparisons are difficult because little information about experimental conditions was provided and statistical analyses were not conducted.

Although the differences in the reinforcing strength of methamphetamine and *d*-amphetamine agreed with epidemiological findings, results for cocaine and methamphetamine were not similarly aligned. Rates of cocaine use and ED visits in the US are considerably higher than those for methamphetamine (Ciccarone, 2011) but the reinforcing strength of cocaine and methamphetamine did not differ in this study. This disparity is consistent with the notion that inferences about abuse potential made from laboratory-based assessments are likely limited to qualitative information (Katz, 1990). Nonetheless, the present demonstrate a separation in the reinforcing strength of methamphetamine and *d*-amphetamine, which could account, at least in part, for differences in their abuse.

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Figure 1.

Number of injections following saline (sal; open square), and various doses of cocaine (squares), *d*-amphetamine (triangles) and methamphetamine (circles) when substituted for the training dose of cocaine. Data are presented as the group mean (methamphetamine $n=4$; *d*-amphetamine $n=4$; cocaine $n=5$). Error bars denote SD. Filled symbols indicate a statistically significant difference in the number of injections compared to saline. Significant differences in the peak number of self-administered *d*-amphetamine injections relative to methamphetamine and cocaine are indicated by an asterisk (*) and a pound symbol (#), respectively.

TABLE 1

Progressive-ratio schedule parameters

<u>Injection</u>	<u>Ratio</u>	<u>Cumulative Resp</u>
1	50	50
2	62	112
3	77	189
4	95	284
5	117	401
6	144	545
7	177	722
8	218	940
9	267	1207
10	328	1535
11	402	1937
12	492	2429
13	602	3031
14	737	3768
15	901	4669
16	1102	5771
17	1347	7118
18	1646	8764
19	2012	10776
20	2458	13234
21	3004	16238