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Effects of 7-day continuous d-amphetamine, methylphenidate, and cocaine treatment on choice between methamphetamine and food in male rhesus monkeys*

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Abstract

Background—Methamphetamine addiction is a significant public health problem for which no Food and Drug Administration-approved pharmacotherapies exist. Preclinical drug vs. food choice procedures have been predictive of clinical medication efficacy in the treatment of opioid and cocaine addiction. Whether preclinical choice procedures are predictive of candidate medication effects for other abused drugs, such as methamphetamine, remains unclear. The present study aim was to determine continuous 7-day treatment effects with the monoamine releaser d-amphetamine and the monoamine uptake inhibitor methylphenidate on methamphetamine vs. food choice. In addition, 7-day cocaine treatment effects were also examined.

Methods—Behavior was maintained under a concurrent schedule of food delivery (1-g pellets, fixed-ratio 100 schedule) and methamphetamine injections (0–0.32 mg/kg/injection, fixed-ratio 10 schedule) in male rhesus monkeys (n=4). Methamphetamine choice dose-effect functions were determined daily before and during 7-day periods of continuous intravenous treatment with d-amphetamine (0.01–0.1 mg/kg/h), methylphenidate (0.032–0.32 mg/kg/h), or cocaine (0.1–0.32 mg/kg/h).

Results—During saline treatment, increasing methamphetamine doses resulted in a corresponding increase in methamphetamine vs. food choice. Continuous 7-day treatments with d-amphetamine, methylphenidate or cocaine did not significantly attenuate methamphetamine vs. food choice up to doses that decreased rates of operant responding. However, 0.1 mg/kg/h d-amphetamine did eliminate methamphetamine choice in two monkeys.

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Conclusions—The present subchronic treatment results support the utility of preclinical methamphetamine choice to evaluate candidate medications for methamphetamine addiction. Furthermore, these results confirm and extend previous results demonstrating differential pharmacological mechanisms between cocaine choice and methamphetamine choice.

Keywords

methamphetamine; choice; methylphenidate; cocaine; amphetamine

1. Introduction

Methamphetamine addiction is a significant and global public health problem. For example, methamphetamine was the most frequently identified phenethylamine and the most frequently reported compound by federal Drug Enforcement Agency laboratories (2014). In addition, the 2013 National Survey on Drug Use and Health, revealed that the number of individuals aged 12 or older who were current users of methamphetamine in 2013 was 595,000 and this number has remained relatively stable over the past decade (SAMHSA, 2014). Currently, there is no Food and Drug Administration (FDA)-approved pharmacotherapy for the treatment of methamphetamine addiction (Brensilver et al., 2013; Carson and Taylor, 2014; Karila et al., 2010). In summary, the prevalence of methamphetamine abuse and absence of effective treatment strategies for methamphetamine addiction suggests a need for preclinical studies in the development and evaluation of potential pharmacotherapies.

One method of preclinical model validation is a reverse translational or “bedside-to-bench” approach where candidate medications have been first evaluated in either human laboratory drug self-administration studies or clinical trials and then subsequently tested in preclinical models to determine concordance of results. The most evident example of this approach in the drug addiction literature has been methadone treatment for heroin addiction (Dole et al., 1966; Griffiths et al., 1975; Negus, 2006). A more recent example of this reverse translation approach might be the demonstration of amphetamine treatment efficacy for cocaine addiction (Grabowski et al., 2001; Negus, 2003). Overall, the good concordance between candidate medication efficacy in clinical trials and subchronic candidate medications treatment effects in preclinical drug vs. food choice procedures for opioids (Haney and Spealman, 2008; Negus and Banks, 2013) and cocaine (Banks et al., 2015; Haney and Spealman, 2008) support the potential extension of this approach to other abused drugs, such as methamphetamine.

Because of the relative success of agonist-based pharmacotherapy approaches for opioids and cocaine, agonist-based approaches for methamphetamine addiction have been the most extensively examined (Brensilver et al., 2013; Karila et al., 2010). In particular, the monoamine uptake inhibitor methylphenidate and the monoamine releaser d-amphetamine have been two of the most extensively evaluated candidate medications in clinical trials outside of bupropion. Methylphenidate treatment effects have been equivocal with three clinical trials (Konstenius et al., 2014; Rezaei et al., 2015; Tiihonen et al., 2007) demonstrating a reduction in amphetamine/methamphetamine use and three clinical trials (Konstenius et al., 2010; Ling et al., 2014; Miles et al., 2013) demonstrating no effect on

amphetamine/methamphetamine use. Furthermore, d-amphetamine treatment efficacy has not been significant in either clinical trials (Galloway et al., 2011; Longo et al., 2010) or a human laboratory methamphetamine self-administration study (Pike et al., 2014). However, there are two potential reasons for these equivocal or negative clinical results. First, some of these clinical trials did not distinguish between enrolled amphetamine-dependent and methamphetamine-dependent individuals. Given potential differences between amphetamine and methamphetamine interactions at the dopamine transporter (Goodwin et al., 2009), there may also be differential treatment sensitivity between these two drug-dependent populations. Second, candidate medication dosing regimens in clinical trials may be restricted for safety reasons. For example, the largest methylphenidate dose (180 mg/day; ~ 0.11 mg/kg/h) (Konstenius et al., 2014) examined was also a clinical trial that reported a treatment effect.

Given that preclinical studies have both greater control over drug exposure and are able to evaluate both a broader dose range and larger doses than in human drug self-administration studies or clinical trials, the present studies were designed to address these two potential reasons for the equivocal clinical trial results. A concurrent schedule of methamphetamine and food pellet presentation was utilized because preclinical choice procedures have been predictive of candidate medication effects for cocaine (Banks et al., 2015) and heroin (Negus and Banks, 2013). Subchronic 7-day d-amphetamine and methylphenidate treatment effects were determined to model treatment regimens in human laboratory drug self-administration studies and clinical trials. Moreover, to the best of our knowledge, subchronic d-amphetamine or methylphenidate treatment effects on preclinical methamphetamine self-administration have not been previously reported. Furthermore, there are reported differences between cocaine choice and methamphetamine choice in monkeys (John et al., 2015) and the degree to which amphetamine treatment differentially alters cocaine choice vs. methamphetamine choice remains unknown. In addition, we also determined continuous 7-day cocaine treatment effects on methamphetamine choice. Previous studies have demonstrated that methamphetamine treatment reduced cocaine use in a clinical trial (Mooney et al., 2009) and reduced cocaine choice in monkeys (Banks et al., 2011). If cocaine treatment did not attenuate methamphetamine choice, this result would further support dissociation of cocaine choice and methamphetamine choice pharmacological mechanisms.

2. Methods

2.1 Subjects

Studies were conducted in total of five adult male rhesus monkeys (*Macaca mulatta*) surgically implanted with a double-lumen catheter (0.76 mm ID × 2.36 mm OD, STI Flow, Morrisville, NC) inserted into a femoral or jugular vein and had an experimental history (Banks and Blough, 2015). Monkeys were maintained on a diet of fresh fruit and food biscuits (Lab Diet High Protein Monkey Biscuits #5045, PMI Nutrition Inc., St. Louis, MO) delivered in the afternoon post-operant behavioral session. Water was continuously available in the housing chamber and a 12 h light-dark cycle was in effect. Monkeys had visual, auditory and olfactory contact with other monkeys throughout the study. Operant procedures and foraging toys were provided for environmental manipulation and enrichment. Videos or music was also played daily in animal housing rooms to provide

additional environmental enrichment. Animal research and maintenance were conducted according to the 2011 Guide for the Care and Use of Laboratory Animals (8th edition) as adopted and promulgated by the National Institutes of Health. Animal facilities were licensed by the United States Department of Agriculture and accredited by the Association for Assessment and Accreditation of Laboratory Animal Care. The Institutional Animal Care and Use Committee approved the research and environmental enrichment protocol.

2.2 Apparatus

The housing chamber served as the experimental chamber and was equipped with a custom operant panel, a pellet dispenser (Med Associates, Model ENV-203-1000, St. Albans, VT), and two syringe pumps (Model PHM-108, Med Associates). One “self-administration” pump delivered contingent methamphetamine injections through one lumen of the catheter. The second “treatment” pump delivered a 0.1 mL saline, d-amphetamine, methylphenidate, or cocaine noncontingent infusion through the second lumen of the catheter at a programmed rate of every 20 minutes from 12:00 p.m. each day until 11:00 a.m. the following morning. The intravenous catheter was protected by a customized stainless steel tether and jacket system (Lomir Biomedical, Malone, NY) that permitted monkeys to move freely in the home chamber. Catheter patency was periodically evaluated by intravenous ketamine (5 mg/kg) administration through one lumen of the double-lumen catheter and after any pharmacological manipulation that produced a decrease in methamphetamine vs. food choice. The catheter was considered patent if intravenous ketamine administration produced muscle tone loss within 10 s.

2.3 Methamphetamine Versus Food Choice Procedure

Daily experimental sessions were conducted from 0900 to 1100 h in each monkey's home chamber as described previously (Banks and Blough, 2015). The terminal choice procedure consisted of five 20-min components, with a different unit methamphetamine dose available during each successive component (0, 0.01, 0.032, 0.1, and 0.32 mg/kg/injection during components 1-5, respectively). Manipulating the injection volume controlled the methamphetamine dose (0, 0.03, 0.1, 0.3, and 1.0 mL/injection, respectively). Components were separated by 5-min timeout periods. During each component, the left, food-associated key was transilluminated red, and completion of the FR requirement (FR100) resulted in 1-g food pellet delivery. The right, methamphetamine-associated key was transilluminated green, and completion of the FR requirement (FR10) resulted in delivery of the intravenous unit methamphetamine dose available during that component. Stimulus lights for the methamphetamine-associated key were flashed on and off in 3s cycles, and longer flashes were associated with higher methamphetamine doses. Monkeys could complete up to a total of 10 ratio requirements on both the food- and methamphetamine-associated keys. Responding on either key reset the ratio requirement on the other key. Completion of each ratio requirement initiated a 30-s timeout, during which all stimulus lights were turned off, and responding had no programmed consequences. Choice behavior was considered stable when the lowest unit methamphetamine dose maintaining greater than 80% methamphetamine vs. food choice varied by 0.5 log units for 3 consecutive days.

Once methamphetamine vs. food choice was stable, test sessions were conducted to determine continuous 7-day d-amphetamine (0.01-0.1 mg/kg/h), methylphenidate (0.032-0.32 mg/kg/h), or cocaine (0.1-0.32 mg/kg/h) treatment effects on methamphetamine vs. food choice. d-Amphetamine and methylphenidate treatments were tested up to doses that either decreased methamphetamine choice or rates of operant responding primarily during components when food was chosen. The 3-day period of saline infusions before each test drug treatment was used as the baseline “+saline.” At the conclusion of each 7-day treatment periods, saline infusions were reinstituted for at least 4 days and until methamphetamine vs. food choice had returned to pretreatment levels. d-Amphetamine, methylphenidate, and cocaine doses were counterbalanced across subjects, but all drug doses were tested before proceeding to testing of a different drug.

2.4 Data Analysis

The primary dependent measures were (1) percent methamphetamine choice, defined as (number of ratios completed on the methamphetamine-associated key ÷ total number of ratios completed)*100 and (2) number of ratio requirements (hereafter referred to as “choices”) completed. The mean of the last 3 days of each experimental condition for each monkey for each of the measures were then plotted as a function of unit methamphetamine dose during the behavioral session. Results were analyzed using a linear mixed-effects analysis with unit methamphetamine dose and treatment drug dose as the fixed main effects and subjects as the random effect. Additional dependent measures collected were total choices, food choices, and methamphetamine choices for the entire behavioral session. The mean of the last 3 days of each experimental condition for each monkey for each of these measures were then plotted as a function of each dependent measure. These results were analyzed using two-way repeated-measures analysis of variance with experimental manipulation and dependent measures as the main factor. Post-hoc comparisons against baseline “+saline” conditions within a given methamphetamine dose were performed using the Dunnett's test following a significant main effect of experimental manipulation or methamphetamine dose × experimental manipulation interaction as appropriate. The criterion for significance was set *a priori* at the 95% confidence level ($p < 0.05$). All analyses were conducted using JMP Pro 11.1.1, SAS, Cary, NC.

2.5 Drugs

(+)-methamphetamine HCl, (–)-cocaine HCl, and (±)-methylphenidate HCl were provided by the National Institute on Drug Abuse Drug Supply Program (Bethesda, MD). d-Amphetamine hemisulfate was purchased from a commercial supplier (Sigma Aldrich, St. Louis, MO). All drug doses are expressed as the salt forms listed above. All drug solutions were passed through a sterile 0.2 µm filter (Millipore, Billerica, MA) before administration.

3. Results

3.1 Stability of baseline methamphetamine vs. food choice

Under baseline “+ saline” conditions when saline was infused through the ‘treatment’ lumen of the double-lumen catheter, methamphetamine maintained a dose-dependent increase in preference over an alternative food reinforcer. When no (0) or small (0.01 and 0.032 mg/kg/

injection) methamphetamine doses (Figure 1A and 2A, 3A, 4A) were available as the alternative, monkeys primarily responded on the food-associated key. As the unit methamphetamine dose increased, monkeys reallocated their behavior away from the food-associated key such that at a unit methamphetamine dose of 0.1 mg/kg/injection dose, behavior was 50% preference for methamphetamine. A larger unit methamphetamine dose (0.32 mg/kg/injection) maintained almost exclusive methamphetamine preference. Figure 1C and Supplemental Figures 1C, 2C, and 3C¹ show total choices, food choices, and methamphetamine choices completed during the behavioral session during saline treatments. On average, monkeys completed 41 of the 50 available total choices with a distribution of approximately 31 food choices and 10 methamphetamine choices.

3.2 Effects of d-amphetamine on methamphetamine vs. food choice

Figure 2 shows continuous 7-day d-amphetamine treatment effects on methamphetamine versus food choice in individual monkeys (n=4) and group mean results are shown in Supplemental Figure 1A². In general, small (0.01 mg/kg/h) and intermediate (0.032 mg/kg/h) d-amphetamine treatment doses tended to increase methamphetamine vs. food choice and produce leftward shifts in the methamphetamine choice dose-effect function. The largest d-amphetamine treatment dose (0.1 mg/kg/h) eliminated methamphetamine choice in two (M1515, M1523) out of four monkeys and increased methamphetamine choice in the two other monkeys (M1514, M1516). Supplemental Figure 1B shows 0.1 mg/kg/h d-amphetamine treatment significantly decreased choices in components when 0.032 and 0.1 mg/kg/injection methamphetamine was available (methamphetamine dose $\times$ d-amphetamine dose: $F_{9,48} = 2.33$, $p = 0.0288$). Supplemental Figure 2C³ shows that 0.1 mg/kg/h d-amphetamine treatment decreased the total number of choices completed per session and indicative of a general reinforcement-independent rate-altering drug effect (d-amphetamine dose: $F_{3,12} = 4.36$, $p = 0.0269$).

3.3 Effects of methylphenidate on methamphetamine vs. food choice

Figure 3 shows continuous 7-day methylphenidate treatment effects on methamphetamine versus food choice in individual monkeys and group mean data are shown in Supplemental Figure 2A⁴. In general, small (0.032 mg/kg/h) and intermediate (0.1 mg/kg/h) methylphenidate treatment doses tended to increase methamphetamine vs. food choice. Treatment with 0.32 mg/kg/h methylphenidate did not alter methamphetamine preference. Supplemental figure 2B⁵ shows 0.32 mg/kg/h methylphenidate treatment significantly decreased choices per component (methylphenidate dose: $F_{3,45} = 8.53$, $p = 0.0001$). Supplemental Figure 2C⁶ also shows that 0.32 mg/kg/h methylphenidate treatment significantly decreased both total choices (methylphenidate dose: $F_{3,12} = 6.55$, $p = 0.0072$) and food choices completed for the entire session (methylphenidate dose: $F_{3,12} = 5.31$, $p = 0.0147$).

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3.4 Effects of cocaine on methamphetamine vs. food choice

Figure 4 shows continuous 7-day cocaine treatment effects on methamphetamine versus food choice in individual monkeys and group mean data are shown in Supplemental Figure 3A⁷. In general, 0.1 mg/kg/h cocaine treatment did not alter methamphetamine choice. When the cocaine treatment dose was increased to 0.32 mg/kg/h, methamphetamine preference was increased in two monkeys (M1515 and M1509) and decreased in another monkey (M1516). Supplemental Figure 3B⁸ and Supplemental Figure 3C⁹ shows cocaine treatment did not significantly alter choices completed per component or total, food, or methamphetamine choices completed for the entire session.

4. Discussion

The present study was designed to determine the utility of subchronic candidate medication treatments and a preclinical methamphetamine vs. food choice procedure to produce concordant results with human laboratory methamphetamine self-administration studies and clinical trials. There were two main findings. First, individual differences were observed during subchronic d-amphetamine treatment with two monkeys showing complete elimination of methamphetamine choice. These results suggest that larger d-amphetamine treatment than those previous utilized may be efficacious in a subset of methamphetamine-addicted individuals. Second, subchronic methylphenidate and cocaine treatment did not attenuate methamphetamine choice. Overall, these results confirm and extend previous findings demonstrating different pharmacological mechanisms of cocaine and methamphetamine reinforcement under a concurrent schedule.

4.1 Baseline methamphetamine choice

Consistent with previous methamphetamine self-administration studies in nonhuman primates (Banks and Blough, 2015; John et al., 2014, 2015) and humans (Kirkpatrick et al., 2012; Pike et al., 2014), increasing methamphetamine doses resulted in an increased preference over an alternative, nondrug reinforcer. In contrast, the present study was inconsistent with two previous rat methamphetamine choice studies (Caprioli et al., 2015; Ping and Kruzich, 2008). Similar inconsistencies of dose-dependent cocaine choice between nonhuman primates (Banks and Negus, 2010) and rats (Cantin et al., 2010) have also been reported. Whether these differences represent potential procedural or species differences in drug vs. nondrug choice remains to be empirically established. However, the dose dependence of methamphetamine choice in monkeys provides an empirical foundation upon which to determine the predictive validity of preclinical methamphetamine choice results to human laboratory and clinical trial results.

4.2 d-Amphetamine treatment effects on methamphetamine choice

Although continuous d-amphetamine treatment did not significantly attenuate methamphetamine vs. food choice, d-amphetamine treatment did eliminate methamphetamine choice in two out of four monkeys. The present results, from a group

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analysis perspective, are consistent with previous human laboratory (Pike et al., 2014) and clinical trials (Galloway et al., 2011; Longo et al., 2010) demonstrating no robust, significant d-amphetamine treatment effect. However, there is a published case report of oral amphetamine substitution treatment reducing illicit methamphetamine use in four out of ten patients (Sherman, 1990). Furthermore, there are other published case reports of oral amphetamine substitution treatment reducing illicit amphetamine use (Charnaud and Griffiths, 1998; Fleming and Roberts, 1994; White, 2000). Although the environmental and genetic determinants remain to be fully elucidated, the present d-amphetamine results in conjunction with the literature suggest amphetamine substitution treatment may have efficacy in a subset of methamphetamine users and that larger amphetamine doses than those previously published in humans may be necessary to unmask an amphetamine treatment effect on methamphetamine use.

Previous preclinical studies have determined treatment effects with monoamine releasers other than d-amphetamine on methamphetamine self-administration. For example, acute methamphetamine (Munzar et al., 1999; Schindler et al., 2011) or phentermine (Munzar et al., 1999) pretreatment attenuated methamphetamine self-administration. Timecourse analysis of d-amphetamine treatment effects did not reveal a significant attenuation of methamphetamine choice on day 1 and d-amphetamine treatment efficacy increased over subsequent treatment days with complete elimination of methamphetamine choice by days 3–4 that was sustained through the seven treatment days. Furthermore, this d-amphetamine treatment effect was greater in magnitude on methamphetamine choice than seven days of saline substitution for one of these monkeys (Banks and Blough, 2015). Individual differences in lifetime methamphetamine intake or experimental history do not readily explain the differential d-amphetamine treatment effects. Future preclinical studies correlating peripheral or central biomarkers with pharmacological treatment efficacy may unmask potential mechanisms regarding the individual subject sensitivity to d-amphetamine treatment.

4.3 Methylphenidate treatment effects on methamphetamine choice

Subchronic treatment with the monoamine uptake inhibitor methylphenidate also failed to significantly attenuate methamphetamine choice in both group and single subject analyses. These methylphenidate treatment results are consistent with a previous acute methylphenidate pretreatment results on methamphetamine self-administration in monkeys (Schindler et al., 2011) and methylphenidate treatment results in clinical trials (Konstenius et al., 2010; Ling et al., 2014; Miles et al., 2013). However, the presents results are inconsistent with other clinical trials demonstrating methylphenidate treatment reduced amphetamine-type stimulant addiction (Konstenius et al., 2014; Rezaei et al., 2015; Tiihonen et al., 2007). One potential explanation could be these three clinical trials (Konstenius et al., 2014; Rezaei et al., 2015; Tiihonen et al., 2007) did not differentiate between amphetamine- and methamphetamine-dependent individuals as only amphetamine-positive urines were assessed. Consistent with this hypothesis of differential methylphenidate treatment effects on amphetamine vs. methamphetamine use, a subsequent larger clinical trial (Miles et al., 2013) that included predominant amphetamine users from Finland and methamphetamine users from New Zealand showed no methylphenidate

treatment efficacy whereas the previous study from predominantly amphetamine users in Finland (Tiihonen et al., 2007) did show methylphenidate treatment efficacy. Furthermore, in the methylphenidate trial that did directly measure methamphetamine in the urine, methylphenidate was without treatment efficacy (Ling et al., 2014). In summary, the present results are consistent with and extend previous preclinical and clinical results demonstrating a lack of methylphenidate treatment efficacy for methamphetamine addiction.

4.4 Implications for methamphetamine addiction medication development research

The absence of a positive medication effect in either human laboratory methamphetamine self-administration studies or methamphetamine clinical trials hinders preclinical model validation. Despite this lack of a positive control, the present results and the broader scientific literature support two methodologies that may enhance the translational predictive validity of preclinical results to clinical outcomes. First, consistent with other preclinical drug vs. food choice studies (Banks and Negus, 2012), a methamphetamine vs. food choice procedure allows for the assessment of both reinforcement-dependent (behavioral allocation) and reinforcement-independent (rate of behavior) treatment effects. Second, the use of subchronic treatment regimens, compared to acute, single dose experiments, also appears to enhance preclinical predictive validity (Banks et al., 2015; Comer et al., 2008; Haney and Spealman, 2008). Overall, given the accumulative evidence of different pharmacological mechanisms between cocaine choice and methamphetamine choice (John et al., 2015), there is a need for preclinical research to develop novel pharmacotherapeutic strategies to treat methamphetamine addiction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Subchronic d-amphetamine treatment decreased methamphetamine choice in two of four monkeys
- Subchronic methylphenidate and cocaine treatment mostly decreased rates of operant behavior
- Preclinical choice results suggest differential behavioral pharmacological mechanisms for methamphetamine choice versus cocaine choice.

Figure 1.

Stability of baseline methamphetamine vs. food choice during continuous saline treatment over the experimental testing period in rhesus monkeys (n=4). (A and B) Abscissa: unit dose methamphetamine in mg/kg/injection (log scale). (A) Left ordinate: percent methamphetamine choice. Right ordinate: percent food choice. (B) Ordinate: choices completed per component. (C) Ordinate: number of choices per session. Abscissa: experiment end point. Panel shows summary data for total choices, food choices, and methamphetamine choices summed across all methamphetamine doses. All points and bars

represent mean $\pm$ SEM obtained during the 3 days preceding each 7-day experimental testing period.

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Figure 2.

Effects of continuous 7-day d-amphetamine (0.01-0.1 mg/kg/h) treatment on choice between methamphetamine and food in four rhesus monkeys. Abscissa: unit dose methamphetamine in mg/kg/injection. Left ordinate: percent methamphetamine choice. Right ordinate: percent food choice. All points represent mean $\pm$ SEM obtained during days 5-7 of each 7-day treatment period. Missing points indicate that the monkey failed to respond during that component.

Figure 3.

Effects of continuous 7-day (±)-methylphenidate (0.032-0.32 mg/kg/h) treatment on choice between methamphetamine and food in four rhesus monkeys. Abscissa: unit dose methamphetamine in mg/kg/injection. Left ordinate: percent methamphetamine choice. Right ordinate: percent food choice. All points represent mean ± SEM obtained during days 5-7 of each 7-day treatment period. Missing points indicate that the monkey failed to respond during that component.

Figure 4.

Effects of continuous 7-day (-)-cocaine (0.1-0.32 mg/kg/h) treatment on choice between methamphetamine and food in four rhesus monkeys. Abscissa: unit dose methamphetamine in mg/kg/injection. Left ordinate: percent methamphetamine choice. Right ordinate: percent food choice. All points represent mean $\pm$ SEM obtained during days 5-7 of each 7-day treatment period.