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Effects of Extended Cocaine Access and Cocaine Withdrawal on Choice Between Cocaine and Food in Rhesus Monkeys

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Chronic drug use may lead to sufficient drug intake to produce dependence and the emergence of abstinence signs during withdrawal. Although withdrawal can increase the reinforcing effects of some drugs (eg opioids), the impact of withdrawal on the reinforcing effects of stimulants like cocaine is less clear. This study used a novel cocaine *vs* food choice procedure to examine the relative reinforcing strength of cocaine before, during, and after exposure to graded levels of extended cocaine access. Responding in four rhesus monkeys was maintained by cocaine (0–0.1 mg/kg/injection) and food delivery under a concurrent-choice schedule during daily 2-h sessions. Under baseline conditions, cocaine maintained a dose-dependent increase in cocaine choice. Subsequently, subjects were exposed to and withdrawn from periods of extended cocaine access, which was accomplished by implementing daily 21-h supplemental sessions of cocaine self-administration in addition to daily choice sessions. During supplemental sessions, cocaine (0.1 mg/kg/injection) was available under a fixed-ratio 10/time-out X schedule, and the duration of the time-out was varied from 30 to 7.5 min. Cocaine intake increased 10-fold to >11 mg/kg/day during exposure to supplemental sessions with the shortest post-injection time-out. However, parameters of cocaine choice were not significantly affected either during or after extended cocaine access. These results do not support the hypothesis that cocaine withdrawal increases the reinforcing strength of cocaine. This differs from results with the opioid agonist heroin and suggests that withdrawal may have different functions in the maintenance of opioid and stimulant abuse.
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INTRODUCTION

Chronic drug exposure can produce a dependent state as indicated by the emergence of abstinence signs during drug withdrawal. The particular constellation of abstinence signs associated with drug withdrawal varies by drug class and may include an increase in the reinforcing effects of drugs within that class in drug self-administration assays. For example, withdrawal in opioid-dependent subjects produces characteristic somatic signs, as well as an increase in the reinforcing effects of opioid agonists as determined using progressive-ratio and concurrent-choice schedules of reinforcement (Griffiths *et al*, 1975; Yanagita, 1978; Carrera *et al*, 1999; Negus, 2006; Negus and Rice, 2009). Insofar as reinforcing effects are predictive of abuse liability, these findings suggest that chronic drug exposure leading to dependence may enhance the abuse liability of some drugs and may contribute to the prevalence of addiction. Moreover, these findings suggest that useful treatments might target mechanisms that underlie dependence- and withdrawal-associated increases in drug reinforcement. For example, we have shown earlier that methadone and other mu-opioid agonists block withdrawal-associated increases in heroin self-administration, and we have suggested that this effect may contribute to the clinical utility of agonist medications for the treatment of opioid dependence (Negus, 2006; Negus and Rice, 2009). In view of these considerations, there may be value in assessing the conditions under which dependence and withdrawal enhance the reinforcing effects of drugs in other drug classes.

Central nervous system stimulants such as cocaine have high abuse liability and maintain problematic levels of abuse. There are currently no FDA-approved medications for the treatment of cocaine abuse (Vocci *et al*, 2005), and medications development might benefit from evaluation of the magnitude and mechanisms of withdrawal-associated changes in cocaine reinforcement. It is now well established that withdrawal from chronic cocaine produces a characteristic set of abstinence signs, although these signs present more subtly than those produced by withdrawal from other abused drugs, such as opioids. For example, Gawin and Kleber (1986) described cocaine withdrawal as a

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'fluctuating clinical syndrome' with symptoms including anhedonia, anxiety, and irritability. Moreover, cocaine abstinence signs and symptoms can be objectively and reliably assessed using the cocaine selective severity assessment (Kampman *et al*, 1998). In preclinical studies, withdrawal from treatment with cocaine doses up to 60 mg/kg/day for 7 days in rats elicited somatic abstinence signs such as tremors, teeth chatters, and head shakes (Malin *et al*, 2000). Furthermore, withdrawal from either contingent or noncontingent extended cocaine exposure produces affective withdrawal signs including anxiogenic-like effects (Basso *et al*, 1999) and decreases in rates of food-maintained responding (Carroll and Lac, 1987; Kleven and Woolverton, 1991) and intracranial self-stimulation (Markou and Koob, 1991; Kenny *et al*, 2003). Finally, these behavioral studies are supported by neurochemical evidence during cocaine withdrawal showing decreased central nervous system glucose metabolism (Hammer *et al*, 1993) and reduced monoamine levels (Weiss *et al*, 1992; Parsons *et al*, 1995) in brain regions associated with reinforcement.

It has been suggested that somatic, affective, and neurochemical signs of cocaine withdrawal might enhance the reinforcing effects of cocaine by setting conditions under which cocaine could prevent or reverse these aversive abstinence signs and thereby function as a 'negative reinforcer' (Ahmed and Koob, 2005; Koob, 2009). Evidence to address this hypothesis is primarily derived from studies using progressive-ratio procedures. For example, increased breakpoints for cocaine were found after some periods of cocaine exposure and withdrawal in rats (Paterson and Markou, 2003; Morgan *et al*, 2002, 2005; Wee *et al*, 2008; Orio *et al*, 2009). However, multiple other regimens of cocaine exposure and withdrawal failed to increase breakpoints maintained by cocaine in rats or nonhuman primates, and in some cases, breakpoints decreased during cocaine withdrawal (Yanagita, 1975; Yanagita, 1980; Li *et al*, 1994; Morgan and Roberts, 2004; Liu *et al*, 2005; Czoty *et al*, 2006). Taken together, these studies provide much weaker evidence for withdrawal-associated increases in cocaine reinforcement than exists for withdrawal-associated increases in opioid reinforcement.

The aim of this study was to examine the effects of extended cocaine access and subsequent withdrawal on the relative reinforcing strength of cocaine using a novel cocaine *vs* food choice procedure in monkeys. The choice procedure was used for two reasons. First, we and others have shown earlier that opioid withdrawal increases choice of heroin or morphine over food in opioid-dependent monkeys (Spragg, 1940; Griffiths *et al*, 1975; Negus, 2006; Negus and Rice, 2009). Consequently, effects of cocaine withdrawal could be examined under conditions similar to those used earlier to study withdrawal-associated increases in opioid reinforcement. Second, the primary-dependent variable in choice procedures (percent drug choice) is a measure of response allocation rather than response rate. As a result, this measure may be less sensitive than progressive-ratio breakpoints or other dependent measures to nonselective effects of drug withdrawal on overall response rates, which might mask withdrawal-induced increases in reinforcing strength (Griffiths *et al*, 1975; Negus, 2003). We hypothesized that exposure to or withdrawal from extended cocaine access would increase choice of cocaine *vs* food.

METHODS

Animals

Studies were conducted in four adult male rhesus monkeys (*Macaca mulatta*) that had been surgically implanted with double-lumen catheters using aseptic procedures as described earlier (Negus, 2003). Monkeys weighed 6–10 kg and were maintained on a diet of multiple vitamins, fresh fruit, and food biscuits (Lab Diet Jumbo Monkey Biscuits, PMI Feeds, Inc, St Louis, MO). Biscuits and vitamins were provided in the morning at approximately 9 a.m., and fruit was provided daily between 4 and 5 p.m. In addition, monkeys received up to 50 1-g banana-flavored pellets (Precision Primate Pellets Formula L/I Banana Flavor, P. J. Noyes Co, Lancaster, NH) during daily operant sessions (see below). Water was continuously available. A 12-h light–dark cycle was in effect (lights on from 7 a.m. to 7 p.m.). All monkeys had prior exposure to the cocaine *vs* food choice procedure and treatment with monoaminergic and/or opioid test compounds (unpublished results). However, this study was the first exposure for any monkey to the extended cocaine access conditions.

Animal maintenance and research were conducted in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health. The facility was licensed by the United States Department of Agriculture, and the Institutional Animal Care and Use Committee approved all protocols. Furthermore, consulting veterinarians periodically monitored the health of the monkeys. Monkeys had visual, auditory, and olfactory contact with other monkeys throughout the study. Operant procedures and foraging toys provided opportunities for environmental manipulation and enrichment. Music or nature videotapes were also played daily in animal housing rooms to provide additional environmental enrichment.

Apparatus and Catheter Maintenance

Experimental sessions were conducted in each monkey's home cage. The front wall was equipped with an operant response panel ($28 \times 28\,cm^2$) that included three circular response keys (5.1 cm in diameter) arranged 2.5 cm apart horizontally. Red, green, or yellow stimulus lights could illuminate each key. Each housing chamber was also equipped with a pellet dispenser (Gerbrands, Model G5210, Arlington, MA) and two syringe pumps (Model BSP-lE, Braintree Scientific, Braintree, MA; or Model PHM-100, Med Associates Inc, St Albans, VT), one for each lumen of the double-lumen catheter. One syringe pump (the 'self-administration pump') was used to deliver self-administered cocaine injections through one lumen of the double-lumen catheter. The second syringe pump was used to deliver saline through the second lumen of the catheter to promote catheter patency. This second pump was programmed to deliver 0.1 ml infusions every 20 min from 10 a.m. each day until 9 a.m. the next morning. From 9 a.m. to 10 a.m. each morning, the health of the monkeys was

inspected, equipment and syringe volumes were checked, and syringes were replaced if necessary. Operation of the operant response panels and data collection were accomplished with microprocessors and software purchased from Med Associates Inc. The intravenous catheter was protected by a tether system consisting of a custom-fitted nylon vest connected to a flexible stainless steel cable and fluid swivel (Lomir Biomedical, Malone, NY). This flexible tether system permitted monkeys to move freely in the cage. Catheter patency was periodically evaluated by i.v. administration of ketamine (5 mg/kg) or the short-acting barbiturate methohexital (3 mg/kg) through the catheter lumen. The catheter was considered to be patent if i.v. administration of ketamine or methohexital produced a loss of muscle tone within 10 s.

Behavioral Procedures

Training procedures. Behavioral sessions were conducted 7 days a week as described earlier (Negus, 2003). After initial shaping of key press responding maintained by food delivery (1-g food pellets) and drug injections (0.1 mg/kg/injection cocaine), choice training was initiated. Choice sessions were conducted during daily 2-h sessions from 11 a.m. to 1 p.m. The terminal choice schedule consisted of five 20-min components separated by 5 min time-out periods (total session duration of 120 min). During each component, the left, food-associated key was illuminated with red stimulus lights, and completion of the fixed-ratio (FR) requirement resulted in the delivery of a food pellet. The right, cocaine-associated key was illuminated with green stimulus lights, and completion of the FR requirement on this key resulted in the delivery of a cocaine dose. A different cocaine dose was available during each of the five successive components (0, 0.0032, 0.01, 0.032, and 0.1 mg/kg/injection during components 1–5, respectively), and dose was varied by varying the duration of pump activation and the resulting volume of each injection. Stimulus conditions on the drug-associated key were also varied by flashing the stimulus lights on and off in 3-s cycles. (Component 1: 0 s on, 3 s off; Component 2: 0.1 s on, 2.9 s off; Component 3: 0.3 s on, 2.7 s off; Component 4: 1 s on, 2 s off; Component 5: 3 s on, 0 s off). Thus, longer flashes (and shorter inter-flash intervals) were associated with higher available drug doses. The response requirements were set at FR 100 on the food-associated key and FR 10 on the cocaine-associated key for all monkeys, because our earlier studies indicated that, under these response requirements, monkeys usually switched from the food-associated key to the drug-associated key during the fourth response period, when an intermediate unit dose of 0.032 mg/kg/injection cocaine was available (Negus, 2003). An ascending dose order was used because we found earlier that dose order had little or no effect on the cocaine choice dose–effect curve (Negus, 2003). Consequently, with the procedures used in this study, it was possible to observe both leftward and rightward shifts in the cocaine choice dose–effect curves that might result from manipulation of experimental variables.

During each component, monkeys could complete up to 10 total ratio requirements on the food- and cocaine-associated keys. Responding on either key reset the ratio requirement on the other key. Completion of each ratio requirement initiated a 30-s time-out, during which all stimulus lights were turned off, and responding had no scheduled consequences. During components when the drug-associated key was not illuminated and a '0' dose of drug was available, responses on this key were still recorded, they still reset the FR requirement on the food-associated key, and completion of the FR requirement still counted as one of the 10 allotted ratios and initiated a 30-s time-out. If all 10 ratio requirements were completed before the 20-min component had elapsed, then all stimulus lights were extinguished and responding had no scheduled consequences for the remainder of that 20-min component. Choice training was considered to be complete when the lowest cocaine dose maintaining at least 80% cocaine choice varied by $\leqslant$0.5 log units for 3 consecutive days.

Testing procedures. Once responding under the choice schedule was stable, daily choice sessions were continued, and additional daily 'supplemental sessions' of cocaine availability were introduced as described below to provide extended access to cocaine self-administration. Procedures for introducing extended cocaine access were identical to procedures used earlier to study effects of dependence and withdrawal associated with extended heroin access on heroin *vs* food choice (Negus, 2006; Negus and Rice, 2009). In this study, daily supplemental sessions began at 1 p.m. (ie, immediately after the choice session) and concluded the next morning at 10 a.m. During this 21-h supplemental session, the cocaine-associated key was illuminated with green lights, and cocaine (0.1 mg/kg/injection) was available under a FR 10/time-out X min schedule. Three time-out values (30, 15, and 7.5 min) were investigated to provide graded levels of extended cocaine access. A 30-min time-out permitted a maximum of 42 injections (4.2 mg/kg) during the 21-h supplemental session, whereas a 15-min time-out permitted a maximum of 84 injections (8.4 mg/kg), and a 7.5-min time-out permitted a maximum of 168 injections (16.8 mg/kg).

Supplemental sessions were studied in a descending order of time-out values (30, 15, and 7.5 min). Sessions using a given time-out period were implemented for a period of 7 consecutive days. At the conclusion of each 7-day period of extended access, supplemental sessions were terminated for a period of at least 7 days and until responding during the choice sessions recovered to baseline levels for at least 3 days. Supplemental sessions with the next time-out value were then implemented for 7 days, and so on. In two cases, exposure to supplemental sessions with the shortest time-out duration (7.5 min) was extended to 8 days, because a sharp but transient reduction in intake occurred on day 7 (a 'crash,' see below).

A goal of this study was to determine whether extended cocaine access or cocaine withdrawal would alter cocaine *vs* food choice in a manner comparable to the way in which heroin withdrawal was shown to alter heroin *vs* food choice (Negus, 2006; Negus and Rice, 2009). However, earlier studies have suggested that withdrawal-associated changes in cocaine self-administration may be delayed and may occur only after a period of complete abstinence from cocaine (Morgan *et al*, 2002). Accordingly, a follow-up

study was also conducted. In this follow-up study, supplemental sessions with a 7.5-min time-out were implemented for 7 days (from days 1–7). At the conclusion of this 7-day period, supplemental sessions were terminated. In addition, cocaine access during daily choice sessions was also withheld for a second period of 7 days (from days 8 to 14). During this time, food continued to be available during all five components of the daily choice sessions, but the cocaine key was not illuminated, and completion of the response requirement on the cocaine key did produce a cocaine injection. On day 15, normal cocaine access was reinstated during daily choice sessions (ie, unit doses of 0, 0.0032, 0.01, 0.032, and 0.1 mg/kg/injection cocaine were available during the five sequential components of daily choice sessions). Behavior was then monitored for an additional 7 days (from days 15 to 21).

Assessment of somatic withdrawal signs. Approximately 1 h before each choice session during periods of cocaine withdrawal, the presence of somatic withdrawal signs was evaluated using a scoring system used earlier to score signs of opioid withdrawal (Negus, 2006; Negus and Rice, 2009). Specifically, eight withdrawal signs were counted as present or absent during each withdrawal assessment, and the total number of withdrawal signs were counted to yield a Withdrawal Score (ie, maximum Withdrawal Score was '8'). The eight signs were lying on bottom of cage, unusually aggressive or lethargic response to investigator, increased vocalization, retching/emesis, diarrhea, penile erection/masturbation, tremor/convulsion, and a category for other unusual behaviors.

Data Analysis

Choice sessions. The primary-dependent variables for each component were (1) percent cocaine choice, defined as (number ratios completed on the cocaine-associated key $\div$ number of ratios completed) $\times$ 100 and (2) the number of ratios completed. These variables were then plotted as a function of cocaine dose. The ED50 value of the cocaine choice dose–effect curve was defined as the dose of cocaine that produced 50% cocaine choice. ED50 values were calculated by interpolation when only two data points were available (one below and one above 50% cocaine choice) or by linear regression when at least three data points were available on the linear portion of the dose–effect curve. Log ED50 values were calculated for each monkey during (1) the last 3 'baseline' days before introduction of each type of supplemental session, (2) the last 3 days of each 7-day period of access to supplemental sessions, and (3) days 1, 4, and 7 after exposure to each type of supplemental session (or days 1, 4, and 7 after the 7-day abstinence period for the follow-up study). Additional dependent variables collected during each session included total choices, total food choices, total cocaine choices, and total cocaine intake.

The initial phase of the study, which examined the effects of extended cocaine access provided through supplemental sessions with different time-out values, was conducted in a group of four monkeys. Baseline data collected before implementation of each type of supplemental session were similar, and these data were averaged for display and analysis. The second phase of the study, which examined the effects of 7 days extended access followed by 7 days of cocaine abstinence, was conducted in a group of three monkeys, and baseline data collected only during this phase of the study were used for display and analysis. Values were compared by one-factor ANOVA, with treatment condition as a within-subjects factor. A significant ANOVA was followed by the Dunnett *post hoc* test to compare test conditions with baseline conditions. The criterion for significance was set at $P<0.05$.

Supplemental sessions. The primary-dependent variables from supplemental sessions were the number of injections per day and the amount of cocaine intake per day in mg/kg. In addition, to provide information on diurnal patterns of cocaine self-administration during supplemental sessions, the number of injections during each quintile of each supplemental session was also determined. The timing of the five quintiles was 1:00–5:12 p.m., 5:12–9:24 p.m., 9:24 p.m.–1:36 a.m., 1:36–5:48 a.m., and 5:48–10:00 a.m.

Drugs

Cocaine HCl (provided by the National Institute on Drug Abuse Drug Supply Program, Bethesda, MD) was dissolved in sterile saline. Drug doses are expressed in terms of this salt form of cocaine.

RESULTS

Baseline Choice Between Cocaine and Food

Figure 1 (top panel, open circles) shows that cocaine maintained a dose-dependent increase in cocaine choice under baseline conditions, when cocaine was available only during daily choice sessions. When low cocaine doses were available (0–0.01 mg/kg/injection), monkeys responded almost exclusively for food, and when higher cocaine doses were available (0.032–0.1 mg/kg/injection), monkeys responded almost exclusively for cocaine. Monkeys usually earned the maximum of 10 reinforcers during each component of the choice session (Figure 1, bottom panel, open circles).

The baseline cocaine choice ED50 value is shown in Table 1. The value shown in Table 1 is the mean of three baseline determinations conducted before the introduction of supplemental sessions with each of the three time-out durations. These baseline data were averaged for display and analysis because baseline dose–effect were stable across determinations. Specifically, baseline choice ED50 values were 0.021 mg/kg (0.011–0.039) before 30-min time-out supplemental sessions, 0.018 mg/kg (0.011–0.031) before 15-min time-out supplemental sessions, and 0.019 mg/kg (0.014–0.025) before 7.5-min time-out supplemental sessions.

Effects of Extended Cocaine Access on Choice Between Cocaine and Food

Figure 1 and Table 1 also show cocaine choice dose–effect curves and ED50 values during periods of extended cocaine access produced by introducing daily, 21-h supplemental sessions of cocaine self-administration with 30, 15, or

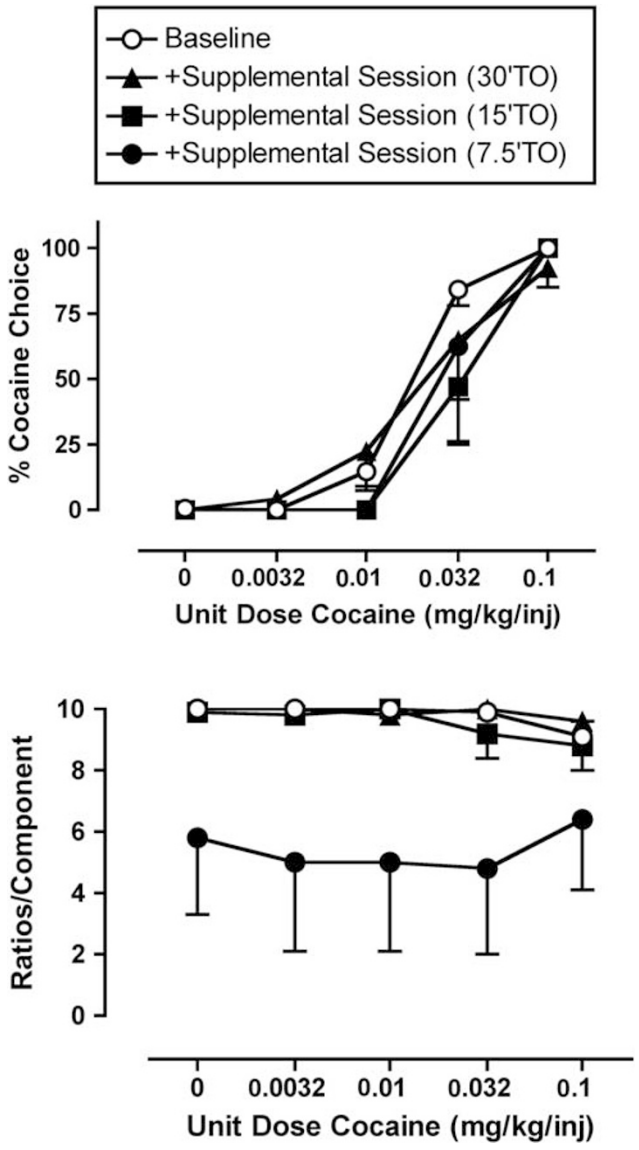

Figure 1 Effects of extended cocaine access on cocaine choice in rhesus monkeys. Abscissae: unit dose cocaine (mg/kg/injection). Ordinate (top panel): % Cocaine choice. Ordinate (bottom panel): number of ratios completed per component (maximum = 10 ratios per component). Extended cocaine access was accomplished by introducing daily, 21-h supplemental sessions of cocaine availability using 30, 15, and 7.5 min post-injection time-out periods. Baseline data show mean results from the 3 days preceding each 7-day period of extended access. Supplemental session data show mean results from the last 3 days of each 7-day period of extended access. All points show mean ± SEM from four monkeys except the filled circles in the top panel (% cocaine choice during exposure to supplemental sessions with 7.5 min post-injection time-outs). These points show data for only 2–3 monkeys, because two monkeys failed to respond during most components and % cocaine choice could not be calculated.

7.5 min time-out periods after each injection. There was a trend for extended cocaine access to produce small rightward shifts in mean cocaine choice dose–effect curves, but extended cocaine access did not significantly alter cocaine choice ED50 values. Extended cocaine access also reduced the numbers of reinforcers/component. During exposure to supplemental sessions with the shortest post-injection time-out (7.5 min), two of the four monkeys failed to respond for either food or cocaine during most components of most daily choice sessions, and responding was also disrupted to a lesser degree in a third monkey.

Table 1 Mean Cocaine ED50 Values in mg/kg (95% CL) Under Baseline Conditions, During 7-day Access to Supplemental Cocaine Self-Administration Sessions with 30, 15, and 7.5 min Post-Injection Time-Outs, and on Days 1, 4, and 7 After Termination of Access to Supplemental Sessions

Condition	Cocaine ED50 in mg/kg (95% CL)
Baseline	0.019 (0.014–0.027)
Supplemental sessions (30′ TO)	
During access	0.021 (0.008–0.058)
Post day 1	0.021 (0.011–0.042)
Post day 4	0.013 (0.004–0.038)
Post day 7	0.013 (0.004–0.039)
Supplemental sessions (15′ TO)	
During access	0.038 (0.023–0.062)
Post day 1	0.031 (0.017–0.059)
Post day 4	0.021 (0.015–0.029)
Post day 7	0.028 (0.016–0.047)
Supplemental sessions (7.5′ TO)	
During access	Not determined[a]
Post day 1	Not determined[a]
Post day 4	0.018 (0.007–0.045)
Post day 7	0.018 (0.018–0.018)

Cocaine ED50 values were not significantly different from baseline either during or after extended cocaine access.
[a]Not determined because rate-decreasing effects prevented calculation of ED50 values in some monkeys.

Patterns of Cocaine Self-Administration During Extended Cocaine Access

Although extended cocaine access had little effect on cocaine choice dose–effect curves, the conditions of extended access did produce dramatic increases in daily cocaine intake. Figure 2 shows the number of injections delivered each day in each monkey during supplemental sessions with post-injection time-outs of 30, 15, or 7.5 min. In general, reductions in the post-injection time-out periods increased the numbers of injections/day. During supplemental sessions with the shortest time-outs (7.5 min), monkeys often responded for >100 injections/day. Reductions in post-injection time-outs also increased the day-to-day variability in cocaine self-administration. This effect was especially prominent in monkeys 21552 and 21786 during supplemental sessions with the shortest post-injection time-out period (7.5 min). For both monkeys, days with high rates of cocaine self-administration alternated with days of little or no self-administration. This type of pattern has been referred to earlier as an 'erratic' or a 'binge-crash' pattern of cocaine self-administration (Deneau *et al*, 1969; Siegel, 1982; Markou and Koob, 1991).

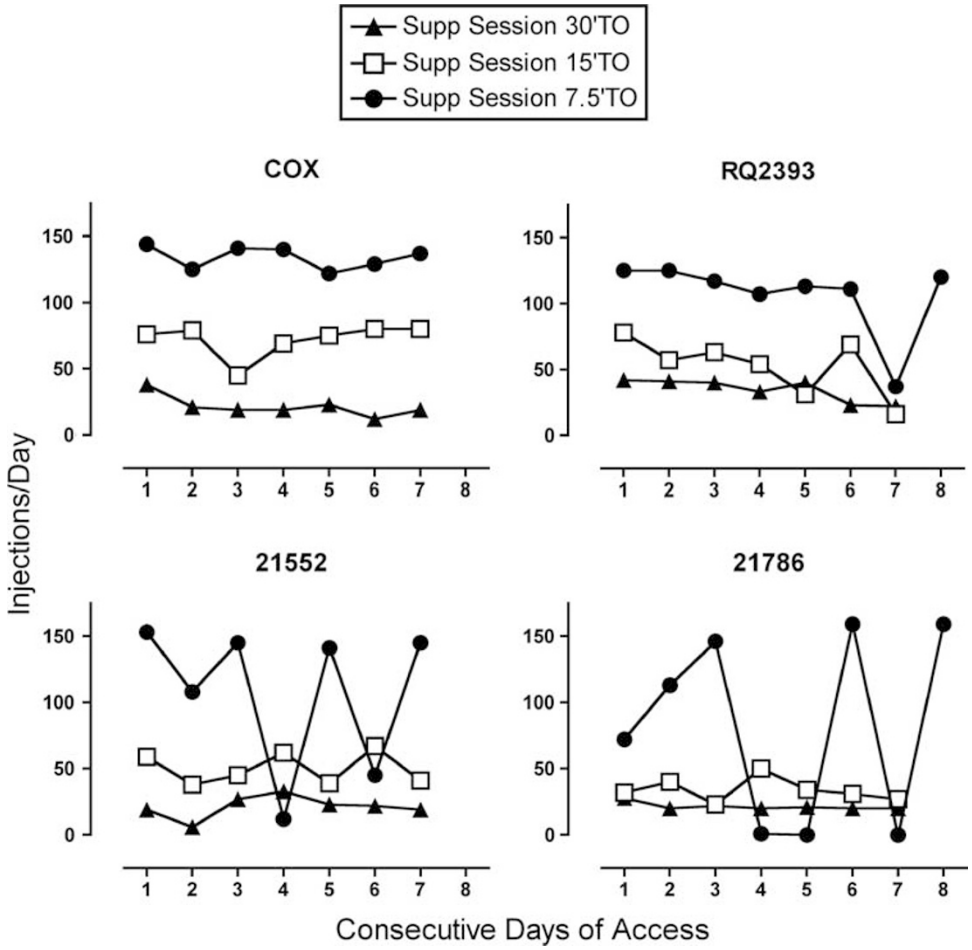

Figure 2 Cocaine self-administration by individual rhesus monkeys during extended cocaine access (supplemental sessions of cocaine availability with post-injection time-outs of 30, 15, or 7.5 min). Abscissae: consecutive days of access. Ordinates: number of cocaine injections (0.1 mg/kg/injection) earned per experimental day. The identification number of each monkey is shown at the top of the panel. Each point shows data from a single determination in one monkey.

Figure 3 (left panel) shows the diurnal pattern of cocaine self-administration across each of the five quintiles of the 21-h supplemental sessions. Reductions in the post-injection time-out period increased rates of cocaine self-administration during each quintile of the supplemental sessions. Diurnal patterns of self-administration were also disrupted. During supplemental sessions with the longest post-injection time-outs (30 min), monkeys self-administered cocaine primarily during the afternoon/evening (quintiles 1 and 2 from 1:00–9:24 p.m.) and during the morning (quintile 5 from 5:48–10 a.m.). Monkeys self-administered very little cocaine at night (quintiles 3 and 4 from 9:24 p.m.–5:48 a.m.). Conversely, during supplemental sessions with the shortest post-injection time-outs (7.5 min), monkeys self-administered cocaine throughout all five quintiles, with a tendency for self-administration to decline across sequential quintiles.

Figure 3 (right panel) shows daily cocaine intake under baseline conditions (choice sessions only) and during extended cocaine access (choice sessions + supplemental sessions). Under baseline conditions, cocaine intake was 1.19 mg/kg/day. Cocaine intake increased with the introduction of supplemental sessions. During access to supplemental sessions with the shortest post-injection time-outs (7.5 min), mean cocaine intake increased approximately 10-fold over baseline levels to 11.57 mg/kg.

Effects of Withdrawal from Extended Cocaine Access on Choice Between Cocaine and Food

Figure 4 shows cocaine choice dose–effect curves determined 1, 4, and 7 days after termination of extended access to cocaine. Cocaine choice ED50 values are shown in Table 1. In general, withdrawal from extended cocaine access had little effect on cocaine choice at any of the time points. In addition, withdrawal from extended cocaine excess failed to elicit any somatic withdrawal signs at any time in any monkey (data not shown). However, there was a time-dependent recovery in the numbers of reinforcers/component after termination of supplemental sessions with 7.5 min post-injection time-outs (Figure 4, bottom right panel).

Effects of Exposure to and Withdrawal from Extended Cocaine Access on Total Choices, Food Choices, Cocaine Choices, and Cocaine Intake

Figure 5 shows the number of total choices, food choices, and cocaine choices, and the level of cocaine intake during

choice sessions conducted under baseline conditions, during extended access to cocaine, and on days 1, 4, and 7 after termination of extended access. Exposure to and withdrawal from supplemental sessions with 30 and 15 min time-outs had little effect on these endpoints. Exposure to supplemental sessions with 7.5 min time-outs reduced total choices, food choices, cocaine choices, and cocaine intake in most monkeys, but this effect did not achieve statistical significance for the group. There was also a tendency for each of these parameters to recover during the 7 days after termination of supplemental sessions.

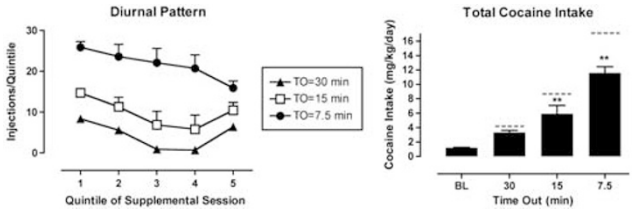

Figure 3 Cocaine intake during periods of extended cocaine access. Left panel: diurnal patterns of cocaine during supplemental sessions of cocaine availability with post-injection time-outs of 30, 15, or 7.5 min. Abscissa: Quintiles of the 21-h supplemental session (Quintile 1: 1:00–5:12 p.m.; Quintile 2: 5:12–9:24 p.m.; Quintile 3: 9:24 p.m.–1:36 a.m.; Quintile 4: 1:36–5:48 a.m.; Quintile 5: 5:48–10:00 a.m.). Ordinate: number of cocaine injections (0.1 mg/kg/injection) during each quintile. Each point shows mean ± SEM from four monkeys during the last 3 days of exposure to each type of supplemental session. Right panel: daily cocaine intake at baseline and during access to supplemental sessions. Abscissa: duration of the post-injection time-out period during the supplemental sessions. The bar above 'BL' shows baseline data when there were no supplemental sessions and cocaine was available only during choice sessions. Ordinate: daily cocaine intake in mg/kg. Baseline data show results from the 3 days preceding each 7-day period of extended access. Supplemental session data show results from the last 3 days of each 7-day period of extended access. All bars show mean ± SEM in four monkeys. Asterisks indicate a significant difference from baseline. $^{**}p < 0.01$. Dashed bar above each supplemental session indicates total possible cocaine intake.

Effects of Withdrawal from Extended Cocaine Access + 7-day Abstinence on Choice Between Cocaine and Food

Figure 6 shows cocaine choice dose–effect curves on days 1, 4, and 7 after (1) a 7-day period of extended access to cocaine (supplemental sessions with 7.5 min post-injection time-outs), followed by (2) a 7-day period of total cocaine abstinence (no cocaine available during either choice or supplemental sessions). Cocaine choice ED50 values are shown in Table 2. As in the initial phase of the study, cocaine maintained a dose-dependent increase in cocaine choice under baseline conditions, and extended cocaine access increased daily cocaine intake (from 1.31 ± 0.01 to 10.11 ± 0.96 mg/kg/day) while having little effect on the cocaine choice dose–effect curve and decreasing the number of ratios completed per component. After termination of extended access, monkeys were exposed to 7 days of cocaine abstinence when only food was available during daily choice sessions, and all monkeys responded for all 50 available food pellets each day during this period of cocaine abstinence. When cocaine choice was reinstated after this period of extended cocaine access and cocaine abstinence, cocaine choice dose–effect curves were similar to baseline dose–effect curves, and cocaine ED50 values were not different from baseline. Total choices, food choices, cocaine choices, and cocaine intake were also similar to baseline levels (data not shown).

DISCUSSION

This study examined effects of exposure to and withdrawal from extended cocaine access on the relative reinforcing

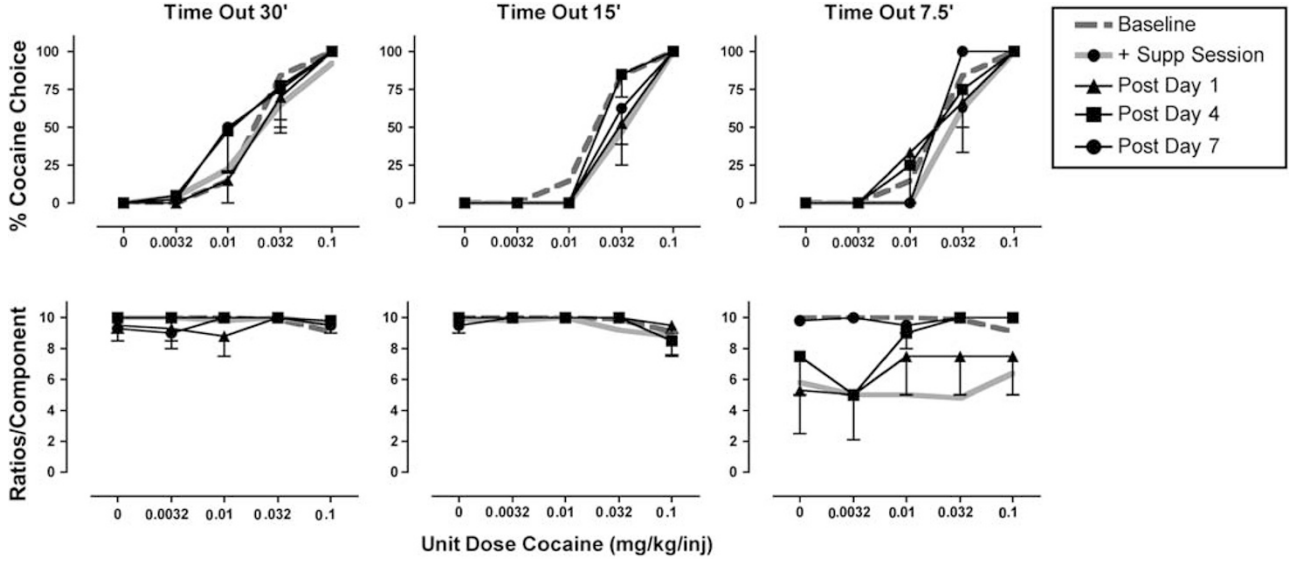

Figure 4 Effects of withdrawal from extended cocaine access on cocaine choice. Abscissae: unit dose cocaine in mg/kg/injection. Ordinates (top panels): percent cocaine choice. Ordinates (bottom panels). Number of ratios completed per component. Data are shown in the left, center, and right panels for supplemental sessions with 30, 15, and 7.5 min post-injection time-outs, respectively. In each panel, baseline data are indicated by a dotted gray line, and data obtained during access to supplemental sessions are shown by a solid gray line (identical to data shown in Figure 1). All points show mean ± SEM data from four monkeys collected on days 1, 4, and 7 after termination of access to supplemental sessions.

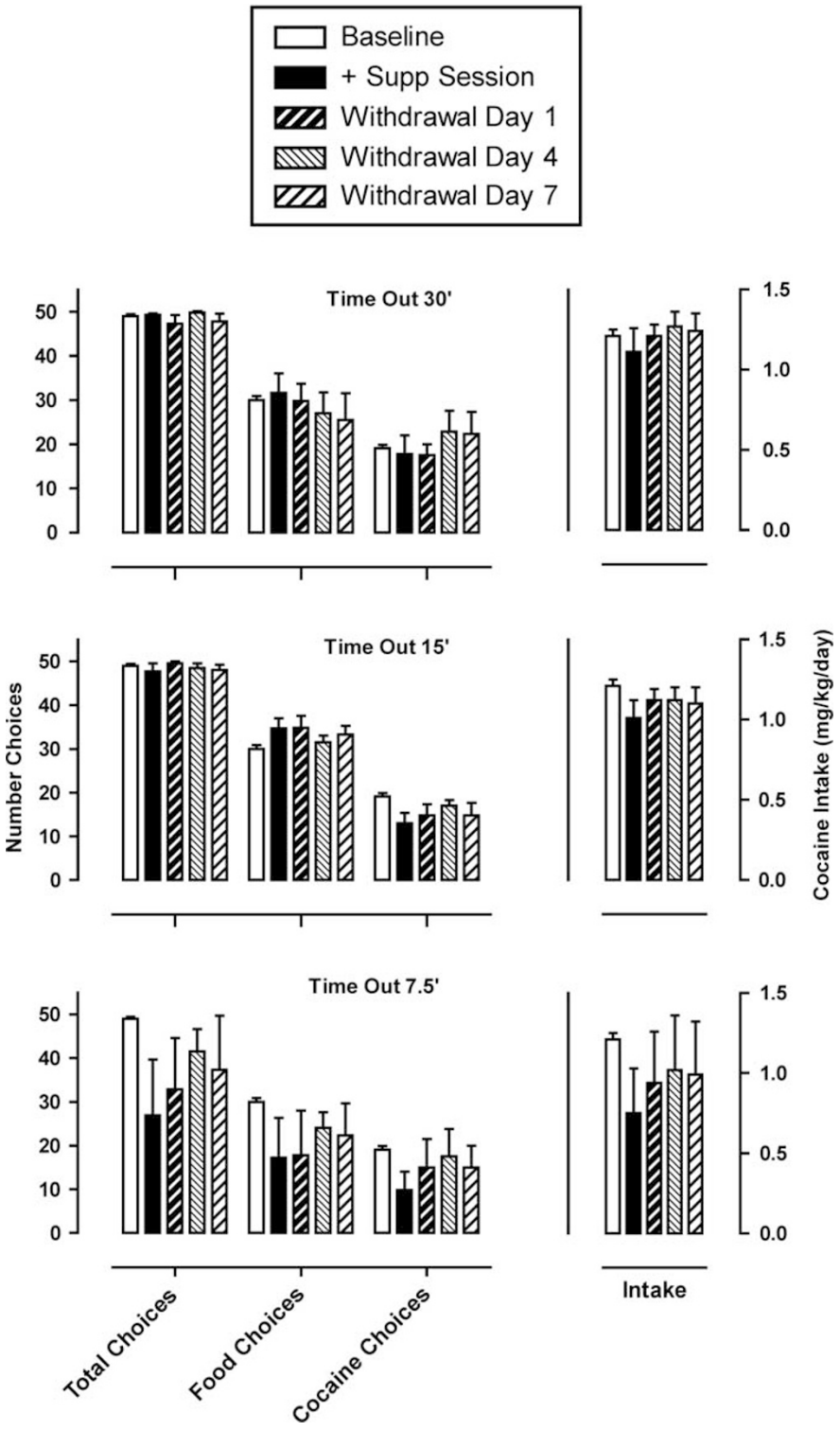

Figure 5 Total choices, food choices, cocaine choices, and cocaine intake during choice sessions before, during, and after extended cocaine access. Abscissae: experimental endpoint. Left ordinates: number of choices per session. Right ordinates: cocaine intake in mg/kg/day during choice sessions. All bars show mean ± SEM data from four monkeys. None of the parameters were significantly different from baseline either during or after extended cocaine access.

strength of cocaine in a cocaine *vs* food choice procedure in rhesus monkeys. Although conditions of extended access were sufficient to maintain high daily cocaine intakes and produce 'binge-crash' patterns of cocaine self-administration, withdrawal did not increase choice of cocaine over food. Consequently, these results do not support the hypothesis that cocaine withdrawal increases the reinforcing strength of cocaine. The relatively modest

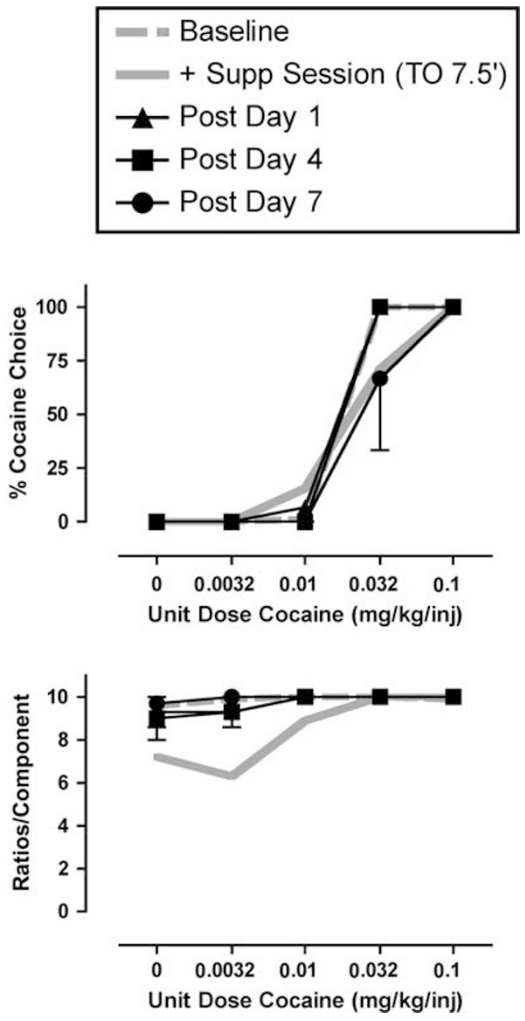

Figure 6 Effects of extended cocaine access +7 days of cocaine abstinence on cocaine choice. Abscissae: unit dose cocaine in mg/kg/injection. Ordinate (top panel): percent cocaine choice. Ordinate (bottom panel). Number of ratios completed per component. In each panel, baseline data are indicated by a dotted gray line, and data obtained during access to supplemental sessions (7.5 min post-injection time-outs) are shown by a solid gray line. All points show mean ± SEM from three monkeys collected on days 1, 4, and 7 after the 7-day abstinence period (ie, days 8, 11, and 14 after termination of access to supplemental cocaine).

effects of cocaine withdrawal on cocaine reinforcement may have implications for both the mechanisms and treatment of cocaine addiction.

Cocaine Choice Before and During Extended Cocaine Access

This study evaluated the relative reinforcing strength of cocaine using a concurrent-choice schedule of cocaine and food availability. Under baseline conditions before introduction of extended cocaine access, cocaine maintained a dose-dependent increase in cocaine choice. These results are consistent with earlier studies of cocaine *vs* food choice in rhesus monkeys (Nader and Woolverton, 1992; Paronis *et al*, 2002; Negus, 2003). Conditions of extended drug access produced graded increases in daily cocaine intakes that were sufficient to decrease the total number of ratios completed during choice sessions. However, there was little change in cocaine choice dose–effect curves during extended cocaine access. These effects produced by contingent cocaine agree with the finding that noncontingent cocaine decreased cocaine self-administration under choice or multiple schedules only at doses that also decreased food-maintained responding (Glowa and Fantegrossi, 1997; Panlilio *et al*, 1998; Negus, 2003).

Table 2 Mean Cocaine ED50 Values in mg/kg (95% CL) Under Baseline Conditions, During 7-day Access to Supplemental Cocaine Self-Administration Sessions 7.5 min Post-Injection Time-Outs, and on Days 1, 4, and 7 After Termination of Access to Supplemental Sessions +7 Days of Cocaine Abstinence

Condition	Cocaine ED50 in mg/kg (95% CL)
Baseline	0.018 (0.018–0.018)
During access	0.023 (0.011–0.047)
Post abstinence day 1	0.017 (0.015–0.019)
Post abstinence day 4	0.018 (0.018–0.018)
Post abstinence day 7	0.026 (0.013–0.055)

Cocaine ED50 values were not significantly different from baseline either during extended cocaine access or after the 7-day abstinence period.

Effects of Cocaine Withdrawal on Cocaine Self-Administration

Drug withdrawal in drug-dependent organisms has long been postulated to promote use of some addictive drugs. However, this study found that withdrawal from extended cocaine access failed to alter the reinforcing strength of cocaine as measured by cocaine *vs* food choice. This finding suggests that drug withdrawal may have a lesser role in regulating the reinforcing strength of cocaine than of other drugs of abuse, such as opioids. Before addressing the implications of this possibility, three other possible explanations for our negative findings should also be considered.

First, one possibility is that drug *vs* food choice is a relatively insensitive measure of reinforcing strength, and that this measure failed to detect changes in the reinforcing strength of cocaine produced by cocaine withdrawal. Two findings argue against this possibility. First, cocaine *vs* food choice in this procedure is sensitive to many other manipulations that are thought to influence the relative reinforcing strength of cocaine, including magnitude of the drug and food reinforcers, FR values for the drug and food choices, noncontingent food delivery, punishment of food or drug choice, treatment with monoamine releasers, and social rank (Negus, 2003, 2004, 2005a, 2005b; Czoty *et al*, 2005). Second, opioid withdrawal in opioid-dependent rhesus monkeys produces a robust increase in choice of opioid agonists over food (Spragg, 1940; Griffiths *et al*, 1975; Negus, 2006; Negus and Rice, 2009). Thus, choice procedures in general are sensitive to many manipulations, and opioid choice is sensitive to opioid withdrawal.

Second, the choice measure in this study provides a relative measure of the reinforcing strength of cocaine in comparison to that of the alternative food reinforcer. As a

result, it is possible that increases in cocaine's reinforcing strength were masked by a concurrent increase in the reinforcing strength of food to produce no net change in choice. Again, two sets of evidence argue against this possibility. First, cocaine withdrawal has been reported to produce either no effect or a decrease in response rates maintained by food (Carroll and Lac, 1987; Woolverton and Kleven, 1988; Branch and Sizemore, 1988; Clark and Poling, 1990) and by other positive reinforcers, such as electrical brain stimulation (Markou and Koob, 1991; Kenny *et al*, 2003). In addition, cocaine withdrawal did not produce significant signs of hyperphagia, hypophagia, or carbohydrate craving in cocaine-dependent humans (Kampman *et al*, 1998). We are aware of no evidence independent of this study to suggest that cocaine withdrawal could increase the reinforcing strength of food and mask increases in the reinforcing strength of cocaine. Second, the results of this study using a choice procedure agree with the preponderance of data from studies that have used progressive-ratio procedures to assess withdrawal-induced changes in the reinforcing strength of cocaine. Thus, in both rats (Li *et al*, 1994; Morgan *et al*, 2002; Morgan, 2004, 2005; Liu *et al*, 2005) and nonhuman primates (Yanagita, 1978, 1980; Czoty *et al*, 2006), withdrawal from chronic exposure to either contingent or noncontingent cocaine usually produced either no change or a decrease in breakpoints maintained by cocaine. For example, Czoty *et al* (2006) examined effects of withdrawal from several different extended cocaine access conditions that resulted in a range of cocaine intakes from 1.2 to 6.9 mg/kg/day, and none of these conditions increased breakpoints maintained by cocaine. Cocaine withdrawal has been reported to increase cocaine-maintained breakpoints in rats under some conditions (Morgan *et al*, 2002, 2005; Wee *et al*, 2008; Orio *et al*, 2009), but these findings have not been representative of the general literature, and the precise determinants of these findings have not been clearly established. Overall, the present results using a choice procedure are consistent with most results from studies using progressive-ratio procedures in finding that cocaine withdrawal usually fails to increase the reinforcing strength of cocaine.

Finally, a third alternative explanation could be that the regimen of cocaine exposure and/or withdrawal was not sufficient to increase cocaine's reinforcing strength. Earlier studies that examined effects of cocaine withdrawal in rhesus monkeys may lend support to this possibility (Woolverton and Kleven, 1988; Kleven and Woolverton, 1991). In these studies, withdrawal from continuous infusion with cocaine disrupted rates of food-maintained responding. However, this abstinence sign was apparent only after treatment with a high dose of 32 mg/kg/day cocaine for 10–35 days. Treatment with lower cocaine doses for shorter treatment times was not sufficient to produce withdrawal-induced decreases in food-maintained responding. In this study, peak intakes of cocaine reached 11.57 mg/kg/day, and these access conditions were implemented for only 7 days at a time. These access conditions were sufficient to engender higher daily cocaine intakes than those tested earlier in studies designed to assess effects of cocaine withdrawal on cocaine self-administration in rhesus monkeys (Czoty *et al*, 2006). Moreover, the cocaine access conditions in this study were sufficient to produce 'binge-crash' patterns of self-administration in 50% of the subjects and reductions in responding maintained by delivery of both cocaine and food during choice sessions. Conditions of greater access (eg, with shorter time-outs) were not tested out of concern for potential convulsive and lethal effects associated with unlimited cocaine access (Deneau *et al*, 1969; Aigner and Balster, 1978). Thus, this study assessed effects of withdrawal from functionally high levels of cocaine self-administration; however, careful studies to assess consequences of higher daily intakes for longer periods may be warranted.

Implications for Mechanisms and Treatment of Cocaine Abuse

The modest effects of cocaine withdrawal on cocaine's reinforcing strength may have implications for both the mechanisms and treatment of cocaine addiction. With regard to mechanism, there is a growing literature to describe both the behavioral and neurobiological consequences of chronic cocaine exposure and withdrawal (Koob, 2009). Moreover, it has been proposed that at least some of these consequences may contribute to addiction by contributing to conditions under which cocaine might serve as a negative reinforcer (Ahmed and Koob, 2005). However, results of this study and other related studies suggest that withdrawal from chronic cocaine may have relatively little effect on cocaine's reinforcing strength. Thus, although consequences of chronic cocaine exposure and withdrawal may be experimentally demonstrable and clinically relevant for overall health, they may have little to do with the maintenance of cocaine use.

With regard to medications development, drug withdrawal in cases of opioid dependence can increase the reinforcing effects not only of the abused opioid agonist (eg, heroin), but also of other opioid agonists that can be used as agonist treatment medications (eg, methadone). The withdrawal-associated enhancement in the reinforcing efficacy of opioid agonist medications may contribute to the relatively high rates of compliance with these medications and high rates of retention in many opioid agonist treatment programs (Kreek *et al*, 2002). By comparison, if cocaine withdrawal produces little change in the reinforcing efficacy of cocaine, then it may also produce little change in the reinforcing efficacy of candidate agonist medications. As a result, agonist-based approaches to the treatment of cocaine addiction may be deprived of a factor that contributes to the success of agonist-based treatments for opioid addiction. This finding may be partly responsible for the relatively low rates of retention in some recent clinical trials with otherwise effective agonist-based medications for cocaine dependence (Grabowski *et al*, 2001, 2004; Mooney *et al*, 2009). However, retention in opioid agonist treatment programs is also variable and influenced not only by the impact of withdrawal on the reinforcing strength of agonist medications, but also by a multitude of other factors related both to medication pharmacology (eg, adequate dosing) and to the environmental setting in which the medication is delivered (eg, contingency management) (Lowinson *et al*, 1997; Rhoades *et al*, 1998; Stitzer and Petry, 2006). Similarly, retention in agonist-based treatment programs for cocaine dependence will also be influenced

by multiple factors, many of which remain to be optimized. Although cocaine withdrawal may have little impact on the reinforcing strength of agonist medications for cocaine dependence, the degree to which this single factor might limit the clinical effectiveness of these medications remains to be determined.

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DISCLOSURE

Negus declares that during the past 3 years he has received compensation as a consultant for or collaborator with the pharmaceutical companies Alkermes, Argolyn, Grunenthal, and Limerick Biopharma for projects related to opioid pharmacology or assessment of abuse liability. This study was not related to any of these professional relationships. Banks declares that except for income received from his primary employer, no financial support or compensation has been received from any individual or corporate entity during the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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