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The Effects of Chronic Cocaine Exposure on Impulsivity in Rats

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Abstract

Chronic exposure to cocaine increases impulsive behavior, leading to a reduced preference for a larger, delayed reinforcer over a smaller, immediate reinforcer. The present study examined the development of impulsivity over multiple days of cocaine exposure and cessation of cocaine. Male Sprague-Dawley rats were trained on a discrete-trials delay-discounting task, during which they chose between a small reinforcer of 1 food pellet immediately and a large reinforcer of 3 food pellets after an adjusted delay (0, 10, 20, 40 60 s). When stable preferences were established, rats received daily injections of deionized water or cocaine (3, 7.5, 15 mg/kg) 5 min prior to the delay-discounting task for 9 days. All groups showed an increased preference for the smaller reinforcer as delay to the larger reinforcer increased. Repeated exposure to 7.5 or 15 mg/kg cocaine further decreased preference for the larger reinforcer over the 9 days. When cocaine administration was discontinued, preference for the larger reinforcer returned to baseline levels in the 7.5 mg/kg group, but remained depressed in the 15 mg/kg group. These findings indicate that continuing exposure to cocaine dose-dependently decreases choice for the large reinforcer over time, that the bias remains when cocaine is no longer administered, and that recovery after high doses of cocaine occurs slowly.

Introduction

Impulsivity is a heterogeneous construct (Pattij and Vanderschuren, 2007) characterized by numerous behaviors including diminished behavioral inhibition, diminished waiting capacity and diminished delay of gratification (Evenden, 1999; Ho et al., 1999). One operational definition of impulsivity is the choice of an alternative with a smaller more immediate consequence over a larger but more delayed consequence. Substance abuse can be considered an act of impulsivity because it involves the choice of small and immediate consequence (e.g., euphoric feeling produced by drug taking), over a larger alternative with a more delayed consequence, (e.g., good health brought about by abstinence; Logue et al, 1992; Pattij and Vanderschren, 2007).

Stimulant medications are commonly used in the treatment of impulse control disorders such as attention deficit hyperactivity disorder (e.g., Chronis et al., 2006; Pattij and Vanderschuren, 2008), and when administered acutely (or in low doses) decrease impulsive behavior in human and non-human animals. However, when administered chronically (or at higher doses), stimulant drugs can increase impulsive behavior (e.g., Evenden and Ryan, 1996; Richards et al., 1999) In particular, the use of cocaine has been shown to increase the

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choice of a small immediate alternative over a larger delayed alternative on delay-discounting tasks in both human and non-human subjects (Logue et al., 1992; Coffey et al., 2003; Paine et al., 2003; Roesch et al., 2008; Perry et al., 2008).

As the delay between reinforcer choice and reinforcer access is increased on delay-discounting procedures, choice for that reinforcer is decreased, or "discounted" as a result (e.g. Ainslie, 1974; Tobin et al., 1993). Increasing the delay to the larger reinforcer increases preference for the smaller more immediate reinforcer (e.g., Rachlin and Green, 1972; Bradshaw and Szabadi, 1992; Tobin et al., 1993). Cocaine-dependent individuals presented with hypothetical money rewards discounted the money more than non-dependent individuals (Coffey et al., 2003). Similarly, chronic exposure to cocaine produced increased preference for smaller, more immediate, food reinforcement in rats (Logue et al., 1992; Paine et al., 2003; Roesch et al., 2007).

In one study, cocaine (15 mg/kg) was administered for 10 to 36 sessions until stable performance was obtained, but only the data from the last 5 days was shown (Logue et al., 1992). Repeated administration of cocaine reduced selection of the larger, delayed food reinforcement, and the effect was reversed when cocaine administration stopped. In another study, cocaine (15 mg/kg x 3 daily) was administered following behavioral testing for 14 days and performance on the delay-discounting task was assessed each morning (Paine et al., 2003). Again, repeated doses of cocaine led to increased preference for shorter delays or smaller reinforcers even though the rats were tested the following morning when cocaine was no longer present. In a third study, cocaine (30 mg/kg i.p.) was administered to rats for fourteen days, in order to induce cocaine sensitization (Roesch et al., 2007). Six weeks following cocaine sensitization, performance on a delay-discounting task was assessed. Rats exposed to chronic cocaine treatment were significantly more sensitive to changes in delay to reinforcement than saline-treated animals. Taken together, these findings suggest that cocaine increases impulsivity on delay-discounting tasks even when rats are not exposed to the behavioral task in the presence of cocaine.

Most of the studies of the effects of cocaine on delay-discounting measured delay-discounting before and after a period of exposure to cocaine. Further, most of the studies tested delay-discounting after the cocaine had been cleared from the subject. These studies allow conclusions about the effects of repeated exposure to cocaine, but do not address how performance is altered when individuals are under the influence of cocaine. Further, whereas studies have examined delay-discounting immediately after chronic cocaine exposure, and at 6 weeks later, no studies have examined how delay-discounting changes over time following discontinuation of cocaine. Therefore, the purpose of the present study was to model the behavior of chronic users who had recently taken cocaine by examining changes in delay-discounting over time during chronic exposure to cocaine and during post-cocaine exposure.

Method

Subjects

Subjects were twenty-four, 90-day old, experimentally naïve male Sprague-Dawley rats. Subjects had free access to water and restricted access to food during testing. Rats were maintained at approximately 85% of their free-feeding weight over the course of the study, housed individually, and exposed to a 12:12 light-dark cycle. Rats were tested 5–7 days a week. All housing and procedures were in accordance with the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council, 2003), and experiments were approved by the Institutional Animal Use and Care Committee of Texas Christian University.

Delay-Discounting Task

The rats were tested in four operant testing chambers (Model #203 1.3, MED Associates, East Fairfield, VT) enclosed in a sound attenuating apparatus, and a fan was mounted on each chamber to provide ventilation and reduce extraneous noise. An IBM-compatible computer was used to run MED-PC 1.15 (MED Associates, East Fairfield, VT), which controlled all experimental events and recorded all lever responses.

Subjects were trained to press levers in a two-lever operant chamber. Following shaping, rats were exposed to a delay-discounting procedure whereby a single lever press to one lever produced one pellet of food immediately, whereas a single lever press to the other lever produced three pellets after an adjusted delay. The general procedure followed that described in Anderson and Woolverton (2005), which is a modified version of the adjusted delay procedure originally created by Evenden and Ryan (1996).

Rats completed one session daily of five sets of choice-trials. Each set consisted of eight trials containing both forced-choice and free-choice trials (for a total of 40 trials per session). The first two trials in every set were forced-choice trials, whereby only the small or large food reinforcer was available. During a forced-choice trial, the house light was turned on, and food reinforcement from only one of the levers was made available (e.g., from the lever associated with the smaller reinforcer), signaled by the light turning on above that lever. The house light was turned off after a choice was made and food was delivered. If a rat did not press the lever after 30 s, the reinforcer corresponding to that lever was automatically delivered. For the second forced-choice trial, reinforcement from the other lever (e.g., the larger reinforcer) was made available. The order of lever presentation during the forced-choice trials was randomized.

Following the two forced-choice trials at the start of every set, the rat was exposed to six free-choice trials. Free-choice trials were identical to forced-choice trials with the exception that lights above both levers were illuminated, giving the rat a choice between simultaneously available larger and smaller reinforcers. Unlike the forced-choice trials, if a rat did not press the lever within 30 s, no reinforcer was delivered, a “null” response was recorded, and the intertrial interval (ITI) was started. The ITIs between all trials (forced and free) were scheduled in such a way that each trial was a total of 90 s long, in order to maintain constant reinforcement frequency across all sessions for all rats.

Training and Baseline Phases—During the first set of 8 trials, the delay to the larger reinforcer was set at 0 s. This delay was then increased in the following order: 1, 2, 4, 6 s. Each delay was in effect for a single set of 8 trials. Following the above delay set, delays to the larger reinforcer were then increased to 0, 2, 4, 8,16 s, followed by 0, 5, 10, 20, 40 s, ending with the terminal values (baseline) of 0, 10, 20, 40, 60 s. Rats were exposed to each delay set for at least 5 sessions and until behavior was stable. Stability was defined as all rats finishing each session with the number choices for the larger reinforcer during the equal-delay condition (0 s) at 80% or more for three consecutive sessions, with less than 20% variation between the number of choices made for the larger reinforcer across these three days.

Following training, rats were exposed to a baseline phase (0, 10, 20, 40, 60 s). Rats were exposed to this phase for at least 5 more consecutive days and until behavior was stable. Twelve of the rats were assigned to a condition in which the right lever always provided the larger reinforcer and the left lever the smaller reinforcer. The other 12 rats were assigned to the left lever condition, whereby the left lever always delivered the larger reinforcer and the right lever the smaller reinforcer.

Drug and Post-Drug Phases—Immediately following the last day of baseline testing, subjects were given a daily injection of cocaine (3, 7.5, 15 mg/kg) or DI (1 ml/kg) five min preceding testing. Drug was administered for 9 consecutive days. Rats were randomly assigned to four groups (six rats per group), whereby each rat received one of the cocaine doses or deionized water. Following the last day of drug administration, subjects continued testing in the delay-discounting task for 14 consecutive days to assess the effects of post-cocaine exposure on impulsive behavior.

Drugs

Cocaine HCl was obtained from Sigma-Aldrich and dissolved in deionized water (DI). Cocaine was administered by i.p. injection (3, 7.5 and 15 mg/kg).

Statistical Analysis

Two dependent variables were used to assess the effects of cocaine on impulsive behavior, the percentage of choices made for the larger reinforcer as a function of delay and rats' indifference points (e.g., Evenden and Ryan, 1996; Paine et al., 2003; Anderson and Woolverton, 2005). Indifference points provide a concise measure of rats' sensitivity to delay, and percentage of choices made for the larger reinforcer gives more detailed information about what choices were made and at what delays. Across all phases of the study, choice for the larger reinforcer was calculated for each rat during free-choice trials by dividing the total number of larger reinforcer choices by the number of larger and smaller reinforcer choices, and multiplying the proportion by 100. Indifference points, or the point at which rats chose each reinforcer 50% of the time, were calculated using the mean number of choices made for the larger reinforcer for rats in each treatment group (DI, 3 mg/kg, 7.5 mg/kg and 15 mg/kg of cocaine). In order to calculate the delay at which rats were indifferent between the larger and smaller reinforcers a regression analysis was performed for each treatment group for choices made across delays (0, 10, 20, 40 and 60 s). Rats' indifference points were calculated using the regression lines.

To ensure that rats did not differ on baseline performance on the delay-discounting task prior to drug administration, a two-way repeated measures analysis of variance (RM ANOVA) was performed on the last 3 days of baseline testing, with cocaine dose (dose) as the between-subjects variable and delay to the larger reinforcer (delay) as the within-subjects variable. In addition, the numbers of omissions (failing to make a choice during a trial) were compared across conditions using one-way ANOVA.

To assess the effects cocaine had on rats' indifference points, a series of one-way RM ANOVAs were performed with treatment group (DI, 3 mg/kg, 7.5 mg/kg and 15 mg/kg of cocaine) as a between-subjects variable and day (2–23) as a within-subjects variable for both the drug and post-drug exposure phases. To assess the effects cocaine had on rats' choice for the larger reinforcer, a three-way RM ANOVA was performed with dose (DI, 3 mg/kg, 7.5 mg/kg and 15 mg/kg of cocaine) as a between-subjects variable and delay (0–60 s) and day (2–23) as within-subjects variables. For within-subject variables, Mauchly's test of sphericity was used, and when appropriate, degrees of freedom were adjusted with the Greenhouse-Geisser epsilon. All significant interactions were assessed for simple effects using individual ANOVAs. When appropriate, Bonferroni post-hoc comparisons were used.

Results

Indifference Points

Indifference points for the drug and post-drug exposure phases were analyzed separately, but plotted together in figure 1 in order to observe changes over time. Indifference points for

day 1 are not shown due to a computer malfunction. There was an effect of dose during the drug administration [F (3, 21) = 6.051, $p = 0.004$] and post-drug exposure [F (3, 39) = 73.228, $p < 0.001$] phases. As seen in figure 1, rats that received 15 mg/kg of cocaine had significantly smaller indifference points during drug administration than did rats that received DI ($p = 0.017$). Rats that received 15 mg/kg of cocaine also had smaller indifference points during cessation from cocaine than rats that received DI ($p < 0.001$), 3 mg/kg of cocaine ($p < 0.001$), or 7.5 mg/kg of cocaine ($p < 0.001$).

Choice for Larger Reinforcer

For a more fine-grained analysis of responding, the rats' responding for the larger reinforcer is shown in figure 2 for the last 3 days of baseline testing (combined), the last day of cocaine exposure (Day 9), the first day of post-cocaine exposure (Day 10) and the last day of post-cocaine exposure (Day 23) for each group of rats. During baseline, choice for the larger reinforcer decreased as delay to reinforcement increased [F (4, 80) = 241.215, $p < 0.001$]. There were no differences between each groups' percentage of choices for the larger reinforcer during baseline [F (12, 4) = 1.269, $p = 0.253$].

When comparing the mean percentage of choices made for the larger reinforcer across all treatment groups, there was an overall effect of delay [F (1.940, 31.045) = 173.315, $p < 0.001$] and day [F (21, 336) = 5.569, $p < 0.001$]. There were also day by dose [F (63, 336) = 1.621, $p = 0.004$], delay by day [F (84, 1344) = 1.484, $p = 0.004$], and delay by day by dose interactions [F (252, 1344) = 1.643, $p < 0.001$]. Rats that received DI or 3 mg/kg of cocaine showed no difference in choice of large reinforcer over time. Rats that received 7.5 mg/kg of cocaine made significantly fewer choices for the larger reinforcer, on the last day of drug exposure (day 9) than during baseline ($p = 0.037$). Rats that received 15 mg/kg of cocaine chose the larger reinforcer significantly less during the first day of post-cocaine exposure (day 10) when the larger reinforcer was delayed 0 s than rats that received DI ($p = 0.024$). Rats that received 15 mg/kg of cocaine also made significantly fewer choices for the larger reinforcer, across all delays, during days 9 ($p = 0.009$) and 10 ($p = 0.038$) than during baseline.

Lever Omissions

All rats omitted responses during forced-choice trials; this behavior was most prominent when delays to the larger reinforcer were high (e.g., 40 & 60 s). There were no significant differences between the number of choices omitted by rats that received cocaine and those that did not [F (3, 20) = 1.626; $p = 0.215$]. Responding for the larger reinforcer was omitted significantly more than the smaller reinforcer ($t = -2.714$, $p = 0.009$). Omissions made during free-choice trials did not vary as a function of delay, but did vary as a function of cocaine dose. Significantly more omissions occurred for rats that received 15 mg/kg of cocaine than for rats in all other conditions [F (3, 20) = 3.231; $p = 0.441$]; however, this effect was produced by the behavior of two of the six rats receiving this dose.

Discussion

In the present study, impulsive behavior was assessed proceeding, during, and for two-weeks following chronic exposure to cocaine (3, 7.5, 15 mg/kg) or DI (1 ml/kg). As expected, rats chose the larger reinforcer less often as delay to its presentation increased. Exposure to cocaine exacerbated this effect. Rats' that received 15 mg/kg of cocaine had significantly smaller indifference points and chose the larger reinforcer significantly less on the delay-discounting task relative to baseline and control animals during the drug administration and post-drug exposure phases. In addition, two of the six rats received 15 mg/kg of cocaine failed to respond on almost half of the trials across all delays. On the first

day of cocaine cessation (Day 10), rats that responded chose the larger reinforcer significantly less even when delay for the larger reinforcer was 0 s. This may suggest that chronic exposure to cocaine led to a reduction in the reinforcing properties of food reinforcement. As days with cocaine exposure increased, a gradual decrease in rats' indifference points occurred, followed by a gradual increase in indifference points following cessation of cocaine.

Overall, findings from the present study are in agreement with past work that chronic cocaine exposure alters choice for reinforcer magnitude on delay-discounting tasks (Logue et al., 1992; Paine et al., 2003; Roesch et al., 2007). The present findings document how chronic exposure to cocaine gradually alters choice for reinforcer magnitude over time. Most studies that have assessed the effects of cocaine on impulsivity have done so either hours (Paine et al., 2003) or weeks (Roesch et al., 2007) following cocaine exposure. Only one study to date has assessed delay-discounting when cocaine was present during testing (Logue et al., 1992); but that study did not assess a time-course of drug action (effects of cocaine across each day of testing). In addition, most studies have only tested a single dose of cocaine (e.g., Logue et al., 1992; Paine et al., 2003).

Previous research (Paine et al., 2003) assessed changes in impulsivity over time following chronic exposure to cocaine, but always administered cocaine the day preceding testing; they reported only a transient decrease in indifference points (on day 7 of 14). In the present study, indifference points gradually decreased (indicating an increase in impulsivity) over days of cocaine exposure in rats that received 7.5 and 15 mg/kg of cocaine. In the present study, cocaine was administered five minutes preceding task completion; in previous work (Paine et al., 2003; Roesch et al., 2007) cocaine was administered hours or days preceding task completion, which suggests that the effects of cocaine on delay-discounting may be time dependent.

When cocaine administration ceased in the present study, indifference points for rats that received 7.5 mg/kg of cocaine recovered to baseline immediately, and rats administered 15 mg/kg of cocaine partially recovered, at best. An earlier study reported full recovery to baseline when cocaine (15 mg/kg) administration ceased (Logue et al., 1992), but another study reported significant increases in impulsive behavior six weeks following chronic exposure to 30 mg/kg of cocaine (Roesch et al., 2007). Rats in the first study (Logue et al., 1992) achieved stability on the discounting task at different rates, which altered the number of days each rat was exposed to cocaine (10–36 days). The measures of impulsivity were collapsed across rats, and derived from the last five stable days of testing during baseline and cocaine administration, therefore effects of time of exposure on the individual rats cannot be assessed. Taken together, these findings suggest that the effects of cocaine on impulsive behavior are dose-dependent, whereby at low doses (7.5 mg/kg) no long lasting effects on impulsivity were seen following cessation of cocaine, and at moderate doses (15 mg/kg) gradual decreases in impulsivity were seen as days without cocaine increased. At higher doses (30 mg/kg), impulsive behavior remained significantly heighted up to six weeks following cessation of cocaine (Roesch et al., 2007).

The purpose of the current study was to assess changes in impulsive behavior on a delay-discounting task during and immediately following chronic exposure to cocaine. Cocaine has been shown to increase impulsive behavior in human (e.g., Coffey et al., 2003; Richards et al., 2007) and non-human animals (Logue et al., 1992; Paine et al., 2003; Roesch et al., 2007). In the present study, chronic exposure to cocaine dose and time-dependently decreased choice for a large reinforcer on a delay-discounting task. Following cessation of cocaine, recovery from the effects of cocaine was again both time and dose-dependent.

These findings imply that treatment of psychostimulant abuse should take into account an increased impulsivity that may last for a substantial period of time.

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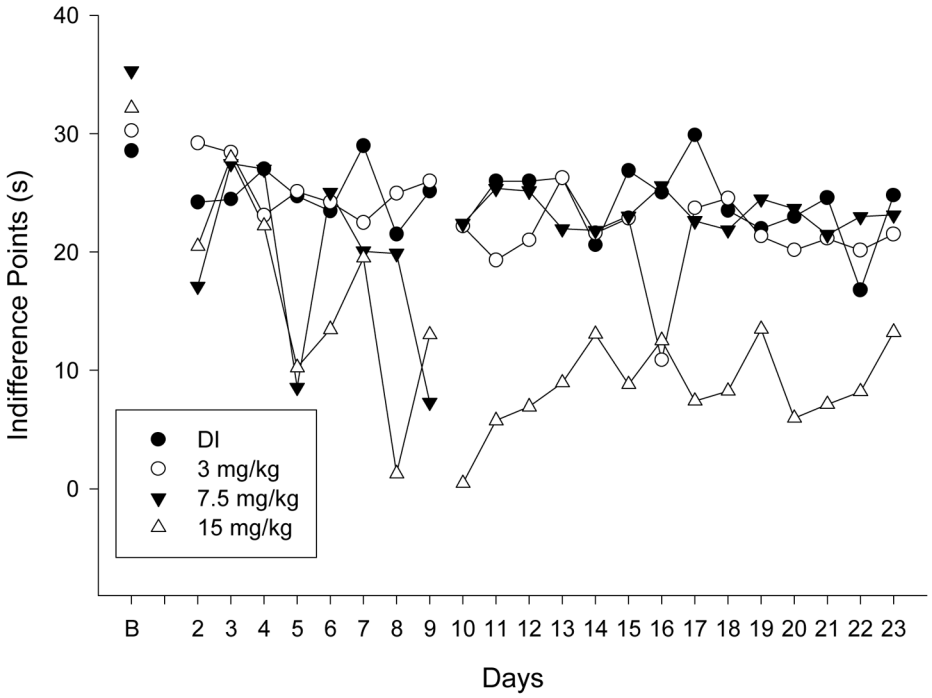

Figure 1.
Indifference points across time. Each point represents the mean indifference point for rats in each drug condition (N = 6). 'B' represents baseline performance prior to drug administration, days 2–9 represent the drug administration phase and days 10–23 represent the post-cocaine exposure phase.

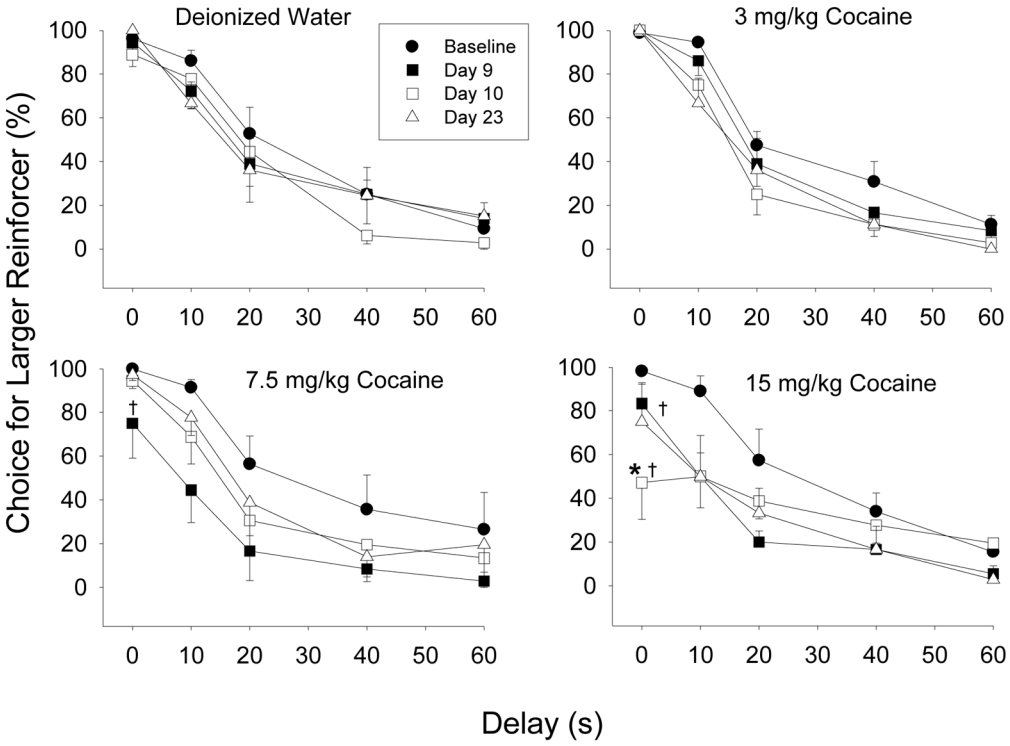

Figure 2.

Percentage of choices made for the larger reinforcer by each group (DI, 3, 7.5 and 15 mg/kg of cocaine) during baseline, the last day of cocaine administration (Day 9), the first day of post-cocaine exposure (Day 10) and the last day of post-cocaine exposure (Day 23). Asterisks (*) indicate points different from those of the DI control animals. Daggers (†) indicate dose functions different from baseline (Day 9 was different from baseline in the 7.5 mg/kg condition, and days 9 and 10 were different from baseline in the 15 mg/kg condition).