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Cocaine exposure causes long-term increases in impulsive choice

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Abstract

This study examined the long-term effects of prior exposure to cocaine on a delay-discounting task commonly used to measure impulsive choice. Male Long-Evans rats received daily i.p. injections of 30 mg/kg cocaine HCl or saline for 14 days. Following three weeks of withdrawal, rats began training. On each trial, rats were given a choice between two levers. A press on one lever resulted in immediate delivery of a single 45 mg food pellet, and a press on the other resulted in delivery of 4 pellets after a delay period. Impulsive choice was defined as preference for the small immediate over the large delayed reward. Three months after treatment, cocaine exposed rats displayed increased impulsive choice behavior. They also showed less anticipatory responding (entries into the food trough) during the delays prior to reward delivery, indicating that the enhanced impulsive choice in these rats may be related to deficits in bridging the delay between response and reward. These data demonstrate that cocaine exposure can cause enduring increases in impulsive choice behavior, consistent with observations in drug-addicted human subjects.

Keywords

delay discounting; cocaine; addiction; decision making; orbitofrontal cortex

Introduction

Drug abuse and addiction are associated with a range of cognitive and neurological deficits, many of which persist long after cessation of drug use (Di Sclafani, Tolou-Shams, Price, & Fein, 2002; Ersche, Clark, London, Robbins, & Sahakian, 2005; Rogers & Robbins, 2001; Volkow & Li, 2004). One aspect of cognition that is affected in addiction is decision making. Decision making in drug addicts is characterized by selection of small short-term gains over larger long-term gains (APA, 2000; Bechara, 2005; Bickel & Marsch, 2001). Such “impulsive choice” may be related to an inability to adequately assess the long-term consequences of one's actions (Bechara, 2005; Dom, Sabbe, Hulstijn, & van den Brink, 2005; Jentsch & Taylor, 1999). This behavioral construct appears to be a factor that can indirectly promote drug addiction (Bechara, 2005; Bickel & Marsch, 2001). Addictive drugs possess immediately reinforcing properties; however, continued use frequently contributes to long-term negative outcomes such as poverty, illness, and social distress. The impaired decision making associated with high levels of impulsive choice may promote selection of the short-term rewards of continued drug use over the long-term benefits (e.g., health, employment, and family)

associated with abstinence (Bechara, 2005; Bickel & Marsch, 2001; Monterosso, Ehrman, Napier, O'Brien, & Childress, 2001).

Despite the strong association between drug addiction and increased impulsive choice, the direction of causation between these two aspects of behavior remains unclear. Several studies in humans (Bickel & Marsch, 2001; Dawes, Tarter, & Kirisci, 1997) and animal models (Mitchell, Reeves, Li, & Phillips, 2006; Perry, Larson, German, Madden, & Carroll, 2005; Poulos, Le, & Parker, 1995) suggest that pre-existing impulsivity may be a causal factor in drug abuse. However, evidence is also mounting to suggest that impulsive choice behavior can be a consequence of drug exposure. Enhanced levels of impulsive choice have been observed in users of nicotine, cocaine, heroin, and alcohol, suggesting that impulsive choice is modulated by current drug use (Bartzokis *et al.*, 2000; Bickel, Odum, & Madden, 1999; Kirby & Petry, 2004). In addition, repeated exposure to drugs of abuse (including cocaine) can produce acute enhancements in impulsive choice in animal models (Logue *et al.*, 1992; Paine, Dringenberg, & Olmstead, 2003; Richards, Sabol, & de Wit, 1999). Together, these data suggest that increased impulsive choice behavior in drug addiction can be a consequence of exposure to the drugs themselves, although this does not preclude a role for pre-existing impulsivity differences in predispositions to drug addiction (Garavan & Stout, 2005).

Abnormal levels of impulsive choice in drug addicts can be exposed through personality inventories and laboratory tests (Bickel & Marsch, 2001; de Wit & Richards, 2003; Kirby & Petry, 2004). Delay discounting, which refers to the manner in which rewards decrease in subjective value (i.e., are “discounted”) in proportion to the delay preceding their delivery, is a measure of impulsive choice used in both human and animal subjects (Cardinal, Winstanley, Robbins, & Everitt, 2004; Petry, 2001). All subjects consistently demonstrate some degree of delay discounting when given the choice between small immediate and large delayed rewards; however, discounting of delayed rewards is considerably greater in drug addicts in comparison to non-addicts (Bechara *et al.*, 2001; Kirby & Petry, 2004; Rogers & Robbins, 2001).

Despite findings that exposure to drugs of abuse can increase impulsive choice behavior acutely, there is only limited evidence that these behavioral deficits persist beyond the cessation of drug exposure (Dallery & Locey, 2005; Roesch, Takahashi, Guga, Bissonette, & Schoenbaum, 2007). The current study investigated whether a regimen of cocaine exposure can produce long-term increases in impulsive choice as assessed in a delay discounting paradigm.

Methods

Subjects

Male Long-Evans rats (n=16, Charles River Laboratories, Raleigh, NC) weighing 275-300 g upon arrival were used for this experiment. Rats were individually housed and kept on a 12 hour light/dark cycle (lights on at 0800) with free access to food and water except as noted. All procedures were conducted in accordance with the Texas A&M University Laboratory Animal Care and Use Committee and NIH guidelines.

Cocaine Exposure

Cocaine HCl was kindly provided by the Drug Supply Program at the National Institute on Drug Abuse. Testing was conducted in 4 identical standard rat test chambers (30.5 × 25.4 × 30.5 cm; Coulbourn Instruments, Allentown, PA) with metal front and back walls, transparent Plexiglas side walls, and a floor composed of steel rods (0.4 cm in diameter) spaced 1.1 cm apart. Each chamber was equipped with an overhead infrared activity monitor for measuring locomotor behavior (Coulbourn Instruments) and was housed in a sound attenuating cubicle.

These chambers were controlled by a computer running Graphic State software (Coulbourn Instruments).

Rats were counterbalanced across saline or cocaine groups ($n=8/\text{group}$) based on locomotor activity during a 60 minute baseline session. After group assignment, the cocaine group received daily i.p. injections of 30 mg/kg cocaine HCl in 0.9% saline at a volume of 1.5 ml/kg for 14 consecutive days. This dose and schedule have been found to produce long-lasting cognitive deficits and locomotor sensitization in previous experiments (Burke, Franz, Gugs, & Schoenbaum, 2006; Mendez *et al.*, 2006; Schoenbaum, Ramus, Shaham, Saddoris, & Setlow, 2004; Schoenbaum & Setlow, 2005; Setlow, Mendez, & Simon, 2006). The saline group received an identical schedule of injections of 0.9% saline vehicle (1.5 ml/kg). Locomotor activity was monitored in the test chambers for one hour immediately following injections. Following this 14 day treatment, all rats were given a three week withdrawal period in which they remained undisturbed in their home cages until the start of behavioral testing.

Behavior

Upon completion of the three week withdrawal period, rats were reduced to 85% of their free-feeding weight over the course of five days and were maintained at this level throughout the duration of behavioral testing. Each test chamber was equipped with a recessed food pellet delivery trough fitted with a photobeam to detect head entries and a 1.12 W lamp to illuminate the food trough. The trough, into which 45 mg grain-based food pellets (PJAI, Test Diet: Richmond, IN) were delivered, was located 2 cm above the floor in the center of the front wall. Two retractable levers were located to the left and right of the food delivery trough, 11 cm above the floor. Locomotor activity was assessed throughout each session with an overhead infrared activity monitor.

The delay discounting procedure was modified from Cardinal, Robbins, and Everitt (2000). On the day before the start of behavioral testing, each rat was given five 45 mg food pellets in its home cage to reduce neophobia to the food. The task began with a 64 minute session of magazine training consisting of 38 deliveries of a single food pellet with an inter-trial interval (ITI) of 100 ± 40 s. On the following day, the rats were shaped to press a single lever (either left or right, counterbalanced across groups; the other was retracted during this phase of training) in order to receive a food pellet (FR1 schedule). Once they reached a criterion of 50 lever presses during a 30 minute session, they were shaped to press the opposite lever with the same schedule and criterion.

Following completion of lever press shaping, both levers were retracted, and rats were shaped to nose poke into the food trough during simultaneous illumination of the trough light and a 1.12 W house light (mounted on the inside back wall of the cubicle, 31.5 cm above the floor). When a nose poke occurred, a single lever was extended, and a lever press resulted in immediate delivery of a single food pellet. Immediately following the lever press, the house and trough lights were extinguished and the lever was retracted. The left and right levers were presented an equal number of times, with no more than two consecutive presentations of the same lever. Rats were trained to a criterion of at least 60 successful trials in an hour with an ITI of 40 ± 10 s. On average, it required 7 days to complete all phases of shaping.

Following shaping, the delay discounting task itself was run for 40 sessions consisting of 5 blocks of 12 trials each. Within each session, each of the 100 s trials began with a 10 s illumination of the food trough and house lights. A nose poke into the food trough during this time extinguished the food trough light and triggered extension of either a single lever (forced choice trials) or of both levers simultaneously (choice trials). Trials on which rats failed to nosepoke during this window were scored as omissions. One rat in the cocaine group was an outlier in its number of omitted trials (11%, which was >2 SD from the group mean of 1%),

and that rat's data were excluded from further analysis (as was the case in Winstanley, Theobald, Dalley, Cardinal, & Robbins (2006)). A press on one lever (either left or right, counterbalanced across groups) resulted in one food pellet being delivered immediately following the lever press. A press on the other lever resulted in delivery of four food pellets after varying delays. Once either lever was pressed, both levers were retracted and the house light was extinguished until food delivery. Food delivery was accompanied by the re-illumination of both lights, which were again extinguished upon entry to the food trough to collect the food or after 10 s, whichever occurred sooner. Each 12 trial block began with two forced choice trials (one for each lever), followed by 10 choice trials. During the first 12-trial block, the delay to the large reward was set at 0 s. In subsequent 12-trial blocks, the delay to the large reward increased to 10, 20, 40, and 60 s. Another rat in the cocaine group displayed a persistent side bias (99% choice of the left lever regardless of delay). This bias persisted even when the lever-reward relationships were reversed (data not shown), and this rat's data were excluded from further analysis (Winstanley, Theobald, Dalley, Cardinal, & Robbins, 2006).

Data Analysis

Raw data files were exported from Graphic State software and compiled using a custom macro written for Microsoft Excel (Dr. Jonathan Lifshitz, Dept. of Anatomy and Neurobiology, Virginia Commonwealth University). Statistical analyses were conducted in SPSS 12.0. Subjects were run in the delay discounting task until stable responding was achieved across a block of six sessions. Stability was defined by the absence of a main effect of days in a repeated measures ANOVA, accompanied by a significant main effect of delay (Cardinal, Robbins, & Everitt, 2000; Winstanley, Theobald *et al.*, 2006). This criterion was first reached during sessions 35-40, which were subsequently used for analysis. Data were averaged across sessions 35-40, and were analyzed using two-way repeated measures ANOVAs (drug condition $\times$ duration of delay). In all cases, p values less than .05 were considered significant.

Results

A baseline level of locomotor activity was initially assessed for all rats during a 60 minute test session, and rats were divided into groups counterbalanced on this measure. There was no difference between groups on this baseline measure ($F_{1,12} = 0.02$). During the 14 days of cocaine administration, rats given cocaine displayed a higher level of activity than rats given saline (Figure 1). A two-factor ANOVA (treatment $\times$ session) revealed significant main effects of treatment ($F_{1,13} = 34.852, p < 0.001$) and session ($F_{13,156} = 2.24, p < 0.01$) on this measure.

In the delay discounting task, there were no differences between groups in total numbers of lever presses, omitted trials, or food trough responses following presentation of the occasion setting stimulus (house and food trough lights); ($F_s < 1$). Analysis of the mean percentage of choices of the large reward across days 35-40 using a two-factor ANOVA (delay $\times$ drug condition) revealed that preference for the large reward lever decreased as the delay to the large reward increased ($F_{(4,48)} = 79.28, p < .01$), demonstrating that delay discounting occurred across all rats. Most importantly, there was a main effect of drug condition ($F_{(1, 12)} = 5.25, p < .05$), such that cocaine exposed rats chose the large delayed reward less often than the saline-treated rats (Figure 2a).

Analyses of food trough entry data revealed that cocaine exposure reliably reduced the proportion of time spent in the food trough during the delays preceding the large reward ($F_{(1,12)} = 5.87, p < .05$); (Figure 2b). There was also an interaction between group and delay duration on this measure ($F_{(3,36)} = 5.30, p < .01$). This reduction was not due to changes in general activity level, as there were no main effects or interactions involving drug condition on locomotor activity during the delay discounting training sessions, either throughout the entire session or only during the delays ($F_s < .02$). There were also no main effects or

interactions involving drug treatment on intra-session measures of motivation, including latency to nose poke upon the presentation of the occasion setting stimuli (house and food trough lights), latency to press the levers following extension, and latency to enter the food trough upon food delivery (F values < 1). Finally, there were no significant Pearson's correlations between cocaine-induced locomotor activity (the increase in locomotor activity from baseline on days 1, 7, or 14) and any of the behavioral measures obtained during the delay discounting task (r values $< \pm .38$).

Discussion

Cocaine exposed rats displayed an increased preference for a small, immediate reward over a large, delayed reward. This effect persisted three months following cessation of drug exposure and is consistent with findings in abstinent cocaine abusers (Heil, Johnston, Higgins, & Bickel, 2006; Kirby & Petry, 2004). In addition, cocaine exposed rats showed a large decrease in responding at the food trough in anticipation of food delivery during the delays preceding the large reward, suggestive of deficits in the ability to bridge the delay between the lever-press response and delayed reward. These results show that exposure to cocaine is sufficient to cause long-lasting increases in impulsive choice behavior, and that this increased impulsive choice may result from impairments in linking responses to outcomes over long delays (Schoenbaum & Roesch, 2005). These drug-induced cognitive alterations could contribute to the maintenance of addictive behavior.

The finding that cocaine exposed rats display increased impulsive choice behavior is consistent with data from human drug addicts. Current drug users choose small, immediate over large, delayed rewards to a greater extent than matched controls (Bechara et al., 2001; Bornovalova, Daughters, Hernandez, Richards, & Lejuez, 2005; Kirby & Petry, 2004), and these deficits have been found to persist during periods of abstinence (Bornovalova et al., 2005; Heil et al., 2006; Kirby & Petry, 2004). The current research supplements the human literature by demonstrating that cocaine exposure can be a causal factor in the increased impulsive choice behavior observed in human drug abusers. It is notable that despite the fact that cocaine was passively-, rather than self-administered (as occurs in humans), the behavioral outcomes were similar to those observed in human drug addicts. This suggests that cocaine exposure itself is more important for the induction of cognitive deficits than the route of administration, although it will be of interest in future experiments to examine the effects of self-administered cocaine on delay discounting.

Rats did not show evidence of sensitization to the locomotor stimulating effects of cocaine across the 14 day cocaine injection regimen. This is not surprising, as the dose of 30 mg/kg cocaine HCl appears to produce a ceiling effect on locomotor activity, effectively preventing observance of potentially enhanced locomotor activity with repeated injections of cocaine. However, we have observed previously that this cocaine regimen does result in locomotor sensitization to challenge injections of cocaine 6 to 8 weeks after cocaine cessation, indicating that the locomotor aspect of sensitization is maintained for long time periods (Schoenbaum et al., 2004; Schoenbaum & Setlow, 2005).

The behavioral alterations in cocaine exposed rats in the delay discounting task were not likely due to a general state of anhedonia or an inability to assess the differences in magnitude between the large and small reward, as there were no differences between groups in latency to collect the food upon delivery, a measure sensitive to changes in reward value (Bohn, Gierler, & Hauber, 2003; Holland & Straub, 1979; Sage & Knowlton, 2000; Schoenbaum & Setlow, 2003). Additionally, during the block of trials in each training session in which there was no delay to the large reward, rats in both groups consistently selected the large reward over the small reward. This indicates that cocaine did not affect rats' ability to detect and respond

appropriately to differences in reward magnitude and that the changes in choice performance were not due to gross alterations in motivation to obtain rewards.

Of particular interest in this experiment was the finding that cocaine exposed rats demonstrated a reduction in time spent performing anticipatory food trough entries during the delay following choice of the large reward lever and preceding reward delivery. In the context of our results, it is possible that the reduction in food trough entries resulted from a cocaine induced working memory deficit - specifically an attenuated ability to represent information about outcomes across delays. Impairment in this aspect of cognition would decrease the ability to recall that a reward will be delivered following a delay, and thus evoke fewer entries into the food trough (Schoenbaum & Roesch, 2005; Schoenbaum & Setlow, 2001). This also offers a potential explanation for the increased impulsive choice behavior observed in this experiment, in that an inability to adequately represent delayed outcomes would render cocaine exposed rats less likely to select delayed rewards over immediate rewards. This hypothesis is consistent with interpretations of similar deficits in cocaine-exposed rats and human drug abusers (Bechara, Dolan, & Hindes, 2002; Schoenbaum & Setlow, 2005). It should be noted that Stefani & Moghaddam (2002) failed to find effects of prior amphetamine exposure on spatial working memory; however, several methodological differences between this and the current study may account for this discrepancy.

Although a deficit in representing delayed outcomes seems a likely explanation for the cocaine-induced behavioral alterations observed here, several other possibilities deserve mention. First, prior experience with cocaine in the training chambers may have influenced subsequent task performance. However, such context conditioning effects (e.g., increased attention to the context and/or increased dopamine release) would be expected to influence multiple performance measures, such as lever press and food collection latencies (through, for example Pavlovian-instrumental transfer (Wyvell & Berridge, 2001)). The fact that cocaine exposure only affected performance measures with a delay component suggests that context conditioning only played a minor role, if any, in the results observed here.

Second, the decreased responding in anticipation of food delivery in cocaine exposed rats may have resulted from an impaired ability to form Pavlovian associations between food predictive stimuli and rewards (Holland & Gallagher, 2004; Pickens *et al.*, 2003). However, there were no differences between groups in latency to respond at the food trough upon presentation of the cue signaling initiation of a new trial, nor were there any differences in total lever presses between groups. Furthermore, previous work suggests that prior psychostimulant exposure (including the cocaine regimen used here) either has no effect on or actually *facilitates* Pavlovian conditioned responses directed toward reward-predictive stimuli (Harmer & Phillips, 1998; Schoenbaum & Setlow, 2005; Taylor & Jentsch, 2001), rendering impaired Pavlovian conditioning an unlikely cause for this result.

A third interpretation of the decreased anticipatory food trough responding is that cocaine exposure affected a different aspect of impulsivity; namely, the ability to inhibit excessive or inappropriate motor responding, or “impulsive action”. Such impulsive action is a separate construct from impulsive choice (Evenden, 1999; Winstanley, Eagle, & Robbins, 2006), and these aspects of impulsivity could be affected in a dissociative manner by cocaine exposure. However, it seems unlikely that impulsive action was decreased in cocaine exposed rats, as there were no differences in any measures of latency to respond to cues or reward, nor were there any differences in the total number of lever presses and omissions between groups. Conversely, it could be argued that the decreased anticipatory time spent in the food trough in cocaine exposed rats resulted from a general *increase* in impulsive action. If anticipatory entry into the food trough is the “appropriate” response during the delay period, then the differences between groups in this measure could result from an attenuated ability to suppress

inappropriate, non-food-directed behaviors. Acute cocaine exposure has been found to reduce behavioral inhibition in rats (Paine & Olmstead, 2004), and impulsive action has also been observed in human drug addicts (Fillmore & Rush, 2002; Hester & Garavan, 2004). However, this effect does not appear to persist past acute cocaine exposure (Dalley *et al.*, 2005). Increased impulsive action was observed in amphetamine exposed rats during withdrawal (Peterson, Wolf, & White, 2003), but this effect only persisted nine days after cessation of drug exposure, making it unlikely that the changes in food trough behavior observed three months after cocaine cessation in this experiment were a result of increased impulsive action. Thus, it appears more plausible that the decreased food trough entries observed were a result of an impaired ability to assess and represent information about delayed outcomes rather than a general change in impulsive action.

The results of this experiment clearly demonstrate that cocaine exposure has long-lasting consequences on neural function. Although the results do not address the neural loci of these functional alterations, animal and human imaging studies suggest that the orbitofrontal cortex (OFC) is a likely candidate. Lesions of OFC result in increased impulsive choice behavior similar to that observed here following cocaine exposure (Mobini *et al.*, 2002; Rudebeck, Walton, Smyth, Bannerman, & Rushworth, 2006). In addition, exposure to cocaine can induce other long-lasting behavioral deficits that are identical to those produced by OFC lesions, such as reversal learning and reinforcer devaluation (Jentsch, Olsson, De La Garza, & Taylor, 2002; Schoenbaum *et al.*, 2004; Schoenbaum & Setlow, 2005). These results are consistent with a large body of literature detailing links between drug addiction and OFC in humans (Bechara *et al.*, 2001; Bolla, Eldreth, Matochik, & Cadet, 2005; Dom *et al.*, 2005; Fillmore & Rush, 2006; Grant, Contoreggi, & London, 2000; Hornak *et al.*, 2004; Rogers *et al.*, 1999; Volkow & Fowler, 2000). The current study offers further behavioral evidence that cocaine may induce OFC dysfunction, although effects on other brain areas obviously cannot be ruled out.

This study is among the first to demonstrate enduring increases in impulsive choice behavior as a result of cocaine exposure (Roesch *et al.*, 2007). The findings are consistent with the human literature showing that the use of a variety of addictive drugs is associated with increased impulsive choice (Bechara *et al.*, 2001; Kirby & Petry, 2004; Rogers & Robbins, 2001). A causal relationship between cocaine exposure and impulsive choice has strong implications for treatment of drug addiction, as prolonged use of drugs such as cocaine would be expected to facilitate the potential for further drug use (selecting the short-term rewards of drug use over the long-term benefits of abstinence), even after long periods of abstinence.

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Figure 1.

Acute effects of cocaine (30 mg/kg) or saline vehicle exposure on locomotor activity. Both groups showed equivalent activity during a non-treatment baseline session (labeled as B on the X axis). Rats given cocaine displayed enhanced locomotor activity compared to saline controls throughout 14 days of treatment.

Figure 2.

(A) Effects of cocaine exposure on choice behavior. Rats exposed to cocaine demonstrated increased impulsive choice (decreased choice of the large reward as the delay to the large reward increased). Data shown are averaged across days 35-40. (B) Effects of cocaine exposure on food trough entry during delays preceding large reward delivery. Rats exposed to cocaine spent a smaller percentage of time nose-poking into the food trough during the delay following choice of the large reward lever and prior to reward delivery. Data shown are averaged across days 35-40.