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Impulsive choice, as measured in a delay discounting paradigm, remains stable after chronic heroin administration

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ABSTRACT

Heroin addicts display poorer impulse control than non-addicts, however it is not known if high impulsivity is a function of chronic heroin intake or a pre-disposing vulnerability for heroin addiction. Using animal models, relatively few studies have examined changes in impulsive choice as a function of chronic drug. The objective of this study was to measure alterations in impulsive choice through a delay discounting paradigm, as a function of chronic heroin administration. Animals were trained on a series of delay discounting sessions. Each session contained 5 blocks of trials. Blocks started with 2 forced, followed by 6 free choice trials. Pressing one lever resulted in the delivery of a small immediate (1 food pellet) reward and another lever in a large delayed (5 pellets) reward. Sessions consisted of the 3 ascending delay sequences in seconds. On the terminal sequence (0, 10, 20, 40, and 60 s) animals exhibited a reversal of reward choice pattern of responding that allowed for the calculation of an indifference point (IP). After animals showed stable IPs they were treated with either heroin or saline for 12 days. Three days after the last injection animals were again placed in operant chambers and experienced the terminal delay discounting sequence at which time IPs were reassessed. Heroin-treated animals exhibited significant progressive increases in locomotor activity. Groups did not differ in IPs or performance across delay conditions during either before or after chronic treatment periods. These results indicate that chronic heroin intake does not impact later impulsive responding for natural (food) reward.

1. Introduction

Maladaptive illicit opiate use, specifically heroin, has been associated with a number of poor outcomes (American Psychiatric Association, 2000) and adverse factors including earlier drug use onset, earlier criminal involvement, longer criminal sentences, and poorer employment histories when compared to long-term cocaine and methamphetamine users (Hser et al., 2008a, 2008b).

Compulsive and maladaptive drug use, in both human and animal populations has been repeatedly associated with impulsive behavior. Impulsive choice is the selection of small immediate rewards over larger delayed rewards (Evenden, 1999). In a choice paradigm where there are two possible rewards, animals repeatedly choose the reward of greater magnitude when delay to reward is equivalent between conditions. However, as delay to the larger reward increases, animals show preference for the smaller, immediately delivered reward.

Human studies comparing active drug users to non-drug using controls have shown a consistent relationship such that drug users more readily discount larger delayed rewards in favor of immediate smaller rewards. These results have been demonstrated in individuals who abuse alcohol (Petry, 2001; Vuchinich & Simpson, 1998), cigarettes (Baker et al., 2003; Mitchell, 1999), cocaine (Coffey et al., 2003), and heroin (Bornovalova et al., 2005; Madden et al., 1999). As these studies are naturalistic by design, it is unclear if differences in choices are due to differences in baseline impulsivity or a result of prolonged and sustained substance use.

Animal studies have shown that differences in baseline impulsivity are associated with later self-administration of ethanol (Poulos et al., 1995; Wilhelm & Mitchell, 2008), d-amphetamine (Cardinal et al., 2000), and cocaine (Belin et al., 2008; Dalley et al., 2007; Perry et al., 2005, 2007, 2008). However, there are relatively few studies examining impulsive choice as a function of drug taking and these studies have generated mixed findings. Paine et al. (2003) reported a transient increase in impulsive choice as a result of cocaine administration in animals previously trained on a delay discounting paradigm. Richards et al. (1999) found that animals decreased impulsive responding when administered acute, non-behaviorally disruptive doses of amphetamine (0.5, 1.0, and 2.0 mg/kg) and exhibited increased impulsivity when the dose was larger (4.0 mg/kg) but administered 22 h before the test session.

Some studies that examined the long-term effects of chronic cocaine administration on impulsive choice found that animals previously exposed to cocaine were significantly more impulsive up to 3 months

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after drug exposure (Simon et al., 2007; Roesch et al., 2007), suggesting that prolonged exposure to large amounts of cocaine results in long-term neural and behavioral adaptations. However, Stanis et al. (2008) showed that while animals receiving 20 days of amphetamine exhibited immediate and long-term locomotor sensitization, they did not display differences in delay discounting when compared to saline-treated animals.

The objective of this study was to measure alterations in impulsive choice behavior, measured through a delay discounting paradigm, as a function of chronic heroin administration. To our knowledge, this is the first study to examine impulsive choice as a function of chronic heroin administration.

2. Methods

The protocols used were in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by the Queens College Institutional Animal Care and Use Committee.

2.1. Animals

Subjects were 25 male Long Evans rats, facility-bred from males and females obtained from Charles River Laboratories (Raleigh, NC), with initial free-feeding weights between 380 and 520 g. Rats were individually housed and maintained on a 12 h light:12 h dark cycle (lights off 0600). Experimental sessions were conducted during the dark phase to test rats during their active periods. Animals had unlimited access to food (Purina rat chow) until the experimental sessions started, at which time access to food was restricted to maintain weights at 85% of free-feeding values.

2.2. Testing apparatus

Instrumental conditioning and delay-discounting sessions were conducted in chambers measuring $30\times22\times27$ cm ($l\times w\times h$) that were housed in ventilated, sound-attenuating boxes. One wall was equipped with two retractable levers with white lights above each lever, and a food trough between levers.

Locomotion was assessed in activity chambers measuring $40.5\times20.5\times24.5$ cm ($l\times w\times h$). Each chamber was equipped with eight photo-emitters positioned along the length of the chamber 6 cm above the floor, each paired directly opposite a photocell.

2.3. Procedure

2.3.1. Training

The delay discounting paradigm was adapted from Evenden and Ryan (1996). Animals were trained to press a lever on a continuous reinforcement schedule where each lever press resulted in the delivery of one food pellet. Sessions lasted 20 min with the right and left levers introduced on alternate days. Training continued until animals pressed for 100 pellets on two consecutive days.

After training, animals were run through a series of 3 delay discounting sessions. Each session contained 5 blocks of trials that were 100 s in duration. Blocks contained 8 trials; 2 forced choice followed by 6 free choice trials. At the onset of the forced choice trial, the right or left lever was randomly introduced and the accompanying light was illuminated. Pressing the left lever resulted in the delivery of a small (1 food pellet) immediate reward. Pressing the right lever resulted in the delivery of a large (5 pellets) delayed reward. During free choice trials, both levers were introduced. After a response or 30 s, levers were retracted and the light was extinguished for the remainder of the trial. Sessions consisted of the following ascending delay sequences: 0, 2, 4, 8, 16 s followed by 0, 5, 10, 20, 40 s, and 0, 10, 20, 40, 60 s. Animals experienced each sequence for a minimum of 7 days and until they exhibited a 3-day average rate of 80% delay lever choice at the 0 s condition. Training was completed when animals exhibited a pattern of performance on the terminal sequence (0, 10, 20, 40, and 60) such that large reward lever responses were reliably below 50% on the larger delay choices. Such performance allowed for the calculation of an indifference point (IP), operationalized as the delay value where the likelihood of responding to either the large or small reward lever was equal. Responding was considered stable when animals exhibited a similar pattern of performance over a period of three consecutive days such that there was a significant difference in delayed reward choices across the 5 blocks of trials.

2.3.2. Experimental phase

After animals completed training and reached a stable IP they were randomly assigned to either saline or heroin groups and placed in activity chambers for 30-min sessions for 12 consecutive days. Animals received intraperitoneal injections of saline for 3 days (habituation) and then received either heroin or saline for the following 9 days (treatment) immediately prior to placement in the activity chambers. Three days following the last injection and activity test, animals were again placed daily in operant chambers where they experienced the terminal delay sequence (0, 10, 20, 40, and 60) and their IPs were reassessed.

2.4. Drug and doses

Heroin (NIDA, Bethesda, MD) was dissolved in saline to achieve a concentration of 2 mg/ml. Solutions were injected in 1 ml/kg volumes.

2.5. Data analysis

Independent sample t-tests were used to assess group differences in before and after-treatment IP. To assess differences in performance across the delay intervals (0, 10, 20, 40, and 60), a 2×5 (group × delay) mixed factorial analysis of variance (ANOVA) was performed on the performance data when animals met criteria for training and at the completion of the study. A 2×2 mixed factorial design was employed to assess for differences as a function of group (between-subjects) across the before and after IP sessions (within-subjects).

Locomotor tests evaluated total beam breaks per 30-minute session. Only data from treatment sessions were analyzed, as habituation sessions (days 1 to 3) did not differ between groups. A 2×9 mixed factorial ANOVA assessed group differences in locomotor activity as a function of group (between-subjects) and session (within-subjects).

3. Results

There were no differences between heroin and saline groups in weight at baseline [$t(1,23)=.21$, $p=.84$] or days to complete the training phase [$t(1,23)=1.47$, $p=.15$]. Before the treatment phase both the heroin and saline groups showed decreases in the likelihood of choosing the large reward as the delay to the large reward increased [see Fig. 1A; $F(4,20)=.44$, $p=.78$] and showed similar IPs [see Fig. 1B; $t(1,23)=.28$, $p=.78$].

During the treatment phase heroin- but not saline-treated, animals demonstrated progressively larger increases in activity across the nine treatment sessions (see Fig. 2). Results of the mixed-design two-way ANOVA revealed a significant session by group interaction [$F(8,16)=6.62$, $p\leq.001$]. Tests of simple main effects revealed a significant session effect for the heroin group [$F(8,7)=8.80$, $p=.005$].

After the treatment phase, tests examining large reward lever presses revealed a significant difference in performance as a function delay [$F(4,20)=83.35$, $p<.01$], but not group [$F(4,20)=.87$, $p=.50$] (see Fig. 3A). Saline- and heroin-treated animals generated similar IPs after the treatment phase [$t(1,23)=.26$, $p=.76$] (see Fig. 3B).

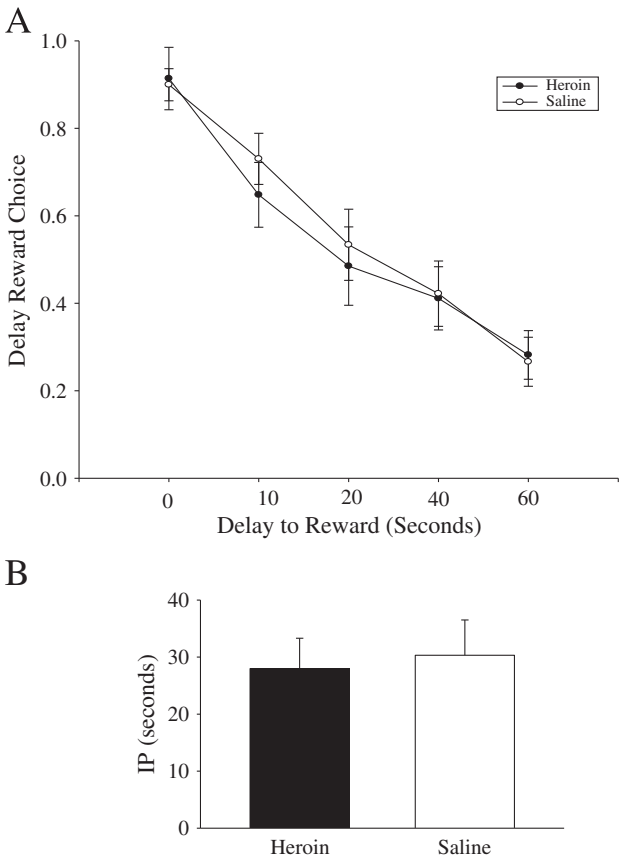

Fig. 1. A: Mean (±SEM) proportions of large reward choices at baseline as a function of delay interval. B: Mean (±SEM) baseline indifference point (s).

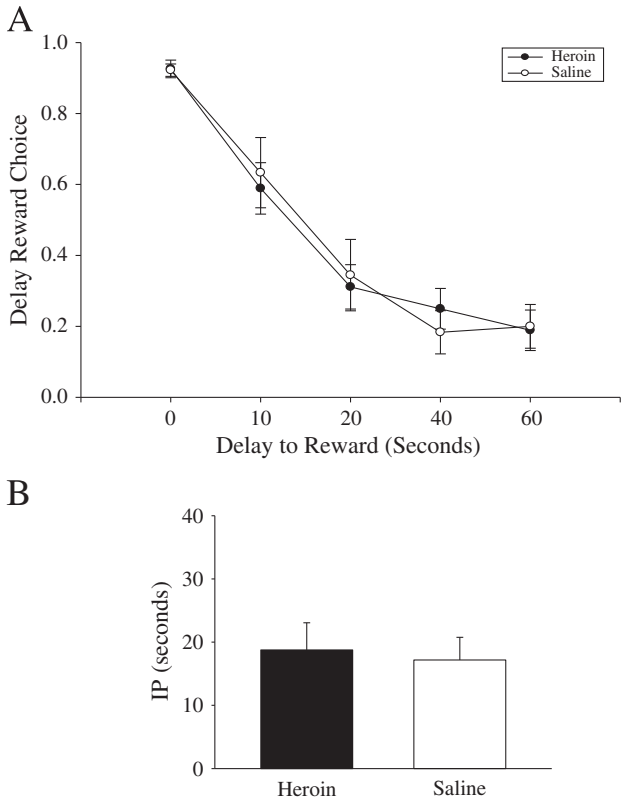

Fig. 3. A: Mean (±SEM) proportions of large reward choices as a function of delay interval and treatment. B: Mean indifference points (s) as a function of chronic heroin or saline treatment.

4. Discussion

This experiment examined the effects of chronic heroin administration on a measure of impulsive choice. Animals exhibited a preference for the larger reward at shorter delay periods and a preference for the smaller reward when delay to the larger reward increased. Heroin- but not saline-treated animals demonstrated progressively greater locomotor activity across the 9-day treatment phase, demonstrating sensitization to the locomotor stimulant effects of the drug. After the treatment phase, animals were again placed in the delay discounting paradigm and IPs were reassessed. Similar to performance before treatment, heroin and saline treated animals did not demonstrate differences in choice behavior across the delay intervals or as measured by the IP.

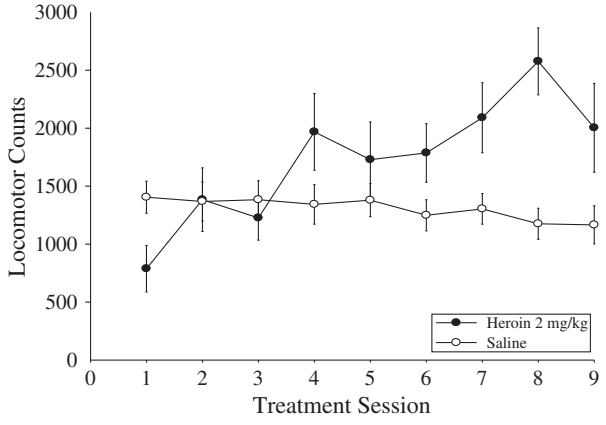

Fig. 2. Mean (±SEM) locomotor counts (beam breaks) per session in groups receiving chronic heroin or saline injections (IP) immediately prior to each session.

Currently, there are only a handful of experiments examining impulsive choice as a function of drug administration and, to our knowledge, this is the first study to examine delay discounting as a function of chronic heroin and sensitization. The primary results of this study indicate that prolonged heroin administration, resulting in sensitization of the locomotor response, does not impact choice behavior as measured by a delay discounting paradigm. The lack of an effect among heroin-treated animals adds to a small literature (Stanis et al., 2008; Winstanley et al., 2007), that indicates that drug use per se does not contribute to increased impulsive choice.

We chose to administer to the animals a dose (2 mg/kg) of heroin that has been shown to result in locomotor sensitization (Ranaldi et al., 2009) and opiate sensitization is associated with long-lasting changes in brain reward systems, namely the dopamine mesolimbic system (Kalivas & Duffy, 1987; Nestby et al., 1997; Spanagel & Shippenberg, 1993; Vanderschuren & Kalivas, 2000). It is unlikely that the current treatment regimen did not produce neuroadaptations in the mesolimbic system. This suggests that whatever aspects of the mesolimbic dopamine system are modified by chronic heroin, they may not be involved in impulsive behavior. However, further research is needed before making more definitive conclusions in this regard.

Taken together, the results of this study do not support the hypothesis that chronic heroin administration results in sustained changes to the processes governing choice behavior. As there are currently only a few existing studies examining the role of chronic drug administration on later impulsive choice, and that these studies have generated dissimilar findings, this study helps to further clarify the impact drug use has on impulsive behaviors, such as impulsive choice. Further, a recent study by McNamara et al. (2010) reported that baseline differences in inhibitory control do not predict differences in heroin self-

administration. Such findings, in combination with those of the current study, suggest that impulsivity may have little to do with heroin abuse.

Our results must be interpreted within the limitations of the study. We measured impulsivity using a delay discounting paradigm where impulsivity was operationalized as the calculated delay to large reward at which the animal shows equal likelihood of choosing the delayed large reward or the immediate small reward (IP). However, impulsivity is a heterogeneous construct (Evenden, 1999) and it is possible animals might exhibit differences on another measure of impulsivity. Additionally, animals received intraperitoneal injections of either heroin or saline. There is evidence to suggest that the mode of administration may differentially impact the degree to which drugs affect the neural systems involved in reward-related behavior (Setlow et al., 2009). It is possible that animals would have performed differently if allowed to self-administer drug.

The limitations listed above are addressed, in part, by a study (Dalley et al., 2005) that also examined the relation between impulsivity and chronic heroin. They operationalized impulsivity as reduced inhibitory control, defined as the frequency of premature responses on a 5-choice serial reaction time task. Additionally, chronic heroin was self-administered as opposed to experimenter-administered as in the present experiment. Similar to the findings generated in the current study, the Dalley et al. (2005) study showed no effect of heroin self-administration on a measure of impulsivity.

5. Conclusion

Chronic heroin administration, resulting in a sensitized locomotor response, does not increase impulsive choice for food reward as measured in a delay discounting paradigm in rats. If such findings generalize to other measures of impulsivity and to human behavior, they would suggest that impulsive characteristics commonly observed in heroin abusers are not secondary to brain changes associated with substance use.

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