Pharmacology, Biochemistry and Behavior 93 (2009) 343–348

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Impulsivity predicts the escalation of cocaine self-administration in rats

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ARTICLE INFO

Available online 31 May 2009

Keywords:
Cocaine
Escalation
Delay discounting
Impulsivity
Rats

ABSTRACT

Impulsivity, as measured by the delay-discounting task, predicts the acquisition of cocaine self-administration and reinstatement of cocaine seeking in rats. The purpose of this study was to extend these results to the escalation phase of drug self-administration. Female rats were initially screened for high (HiI) or low (LoI) impulsivity for food reinforcement using a delay-discounting procedure. They were then implanted with i.v. catheters and trained to lever press for cocaine infusions (0.8 mg/kg). Once cocaine intake stabilized, rats were allowed to self-administer cocaine (0.4 mg/kg) under a fixed-ratio 1 (FR 1) schedule during three, 2 h short-access sessions. Subsequently, performance was briefly assessed under a progressive ratio (PR) schedule for 3 doses of cocaine (0.2, 0.8, and 3.2 mg/kg). Following PR testing, the cocaine dose was then changed to 0.4 mg/kg. Session length was then extended to 6 h for 21 days (extended access), and 0.4 mg/kg cocaine was available under a FR 1 schedule. After the 21-day extended access phase, responses and infusions under the short access FR and PR dose–response conditions were reassessed. The results indicated that HiI rats escalated cocaine-reinforced responding during the extended access condition, but LoI rats did not. HiI rats also earned significantly more infusions than LoI rats under the post-escalation short access FR condition. However, HiI and LoI rats did not differ under the pre- and post-extended access PR conditions. This study suggests that individual differences in impulsivity predict escalation of cocaine self-administration in female rats, which may have implications in the prediction of binge-like patterns of cocaine intake in women.

1. Introduction

Impulsivity is a personality trait related to deficits in inhibition and decision making, and can be viewed on a continuum along which low impulsivity levels are advantageous in certain circumstances (Eysenck and Eysenck, 1977), while high levels are often maladaptive and implicated in the etiology of psychiatric illness (Moeller et al., 2001; Winstanley et al., 2006). Recently, impulsivity has emerged as a major risk factor in the vulnerability to several aspects of drug abuse (for reviews see Acton, 2003; Ivanov et al., 2008; Kreek et al., 2005; Verdejo-Garcia et al., 2008; Wilens, 2007). The relationship between impulsivity and stimulant abuse is especially robust. For example, stimulant abusers exhibit higher levels of impulsivity (relative to non-drug-using controls) as assessed by self-report (Coffey et al., 2003; Moeller et al., 2001, 2002; Patkar et al., 2002; Rosenthal et al., 1990) and behavioral laboratory measures (Coffey et al., 2003; Fillmore and Rush, 2002; Moeller et al., 2002), and the severity of these measures corresponds with stimulant abuse symptoms (Lejuez et al., 2007; Patkar et al., 2004; Poling et al., 2007).

Impulsivity is a multidimensional construct, and two of its most prominent aspects are difficulty in withholding a prepotent response (i.e., impaired response inhibition) and the inability to efficiently adapt behavior in response to changes in delay to reward and/or reward magnitude (i.e., impulsive choice) (de Wit, 2009). These forms of impulsivity are measured by different behavioral tasks, and they have been suggested to be nonoverlapping and mutually exclusive on both a behavioral and neurobiological level (de Wit, 2009; de Wit and Richards, 2004; Winstanley et al., 2004). For example, performance on tasks measuring response inhibition such as the Go/No-Go and stop signal reaction time (SSRT) tasks are mediated by the anterior cingulate cortex and infralimbic cortex, while impulsive choice, as measured by the delay discounting procedure, is sensitive to orbital prefrontal cortex disruption (Dalley et al., 2008; Winstanley et al., 2006). Further, performance on tasks measuring impaired response inhibition does not strongly correlate with performance on tasks measuring impulsive choice (McDonald et al., 2003; Sonuga-Barke, 2002; Winstanley et al., 2004). However, Robinson and colleagues (2009) found a correlation between impulsive performance on the 5-choice serial reaction time (5-CSRT) task and the delay-discounting task (Robinson et al., 2009), but they did not find concordance between delay discounting and the SSRT task (Robinson et al., 2009). Despite this apparent divergence, both forms of impulsivity are related to substance abuse symptomatology in clinical populations (Bornovalova et al., 2005; Coffey et al., 2003; Ersche et al.,

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doi:10.1016/j.pbb.2009.05.013

2008; Heil et al., 2006; Kirby and Petry, 2004; Li et al., 2006; Verdejo-García et al., 2006, 2007).

Animal models provide a means to prospectively evaluate the influence of both impaired response inhibition and impulsive choice on several aspects of drug abuse. For example, rats selected for poor inhibitory control on the 5-CSRT task made more responses during the acquisition of nicotine self-administration (Diergaarde et al., 2008) and self-administered larger amounts of cocaine (Dalley et al., 2007) compared with those selected for good inhibitory control. Rats screened for high levels of impulsive choice on a delay-discounting task subsequently self-administered more ethanol (Poulos et al., 1995) and i.v. nicotine (Diergaarde et al., 2008), acquired cocaine self-administration faster (Perry et al., 2005, 2008), and exhibited greater reinstatement of cocaine-seeking (Perry et al., 2008) than those with low levels of impulsive choice (for review see Carroll et al., in press; Perry and Carroll, 2008). These studies suggest that both impaired response inhibition and impulsive choice are related to heightened drug seeking during critical phases of addiction.

The transition from steady to dysregulated, excessive, and potentially lethal drug consumption characterizes the escalation phase of the drug abuse process (Ahmed and Koob, 1998, 1999; Lynch et al., 2000), and impulsivity may be an important contributor in this transition (Dalley et al., 2007). In studies with rats (Ahmed and Koob, 1998, 1999), escalation was modeled by allowing extended access vs. short access to drug self-administration, defined as 6–12 h vs. 1–3 h, respectively. During extended access, rats exhibited a dramatic increase in drug self-administration that escalated over subsequent sessions. In a study by Dalley et al. (2007), poor inhibitory control on the 5-CSRT was a strong predictor of increased escalation of cocaine self-administration in cocaine-naïve rats indicating that deficits in inhibitory control were related to vulnerability to engage in binge-like drug intake.

The goal of the present study was to examine the influence of another aspect of impulsivity (i.e., impulsive choice as measured by a delay-discounting task) on the escalation of cocaine self-administration in rats. Rats were initially selected for high (HiI) or low (LoI) impulsivity using an adjusting delay-discounting task adapted from Mazur (1987). Pre- and post-extended access cocaine infusions were compared during short access conditions under a fixed-ratio 1 (FR 1) schedule, and dose–response functions were also compared using a progressive-ratio (PR) schedule to evaluate motivation (e.g., Paterson and Markou, 2003) for cocaine self-administration before and after extended access. Based on results from other studies examining the acquisition (Perry et al., 2005) and reinstatement (Perry et al., 2008) of cocaine-seeking behavior in HiI and LoI rats, it was hypothesized that HiI rats would be more at risk than LoI rats for escalation of cocaine self-administration and subsequent elevations of FR 1 and PR performance.

2. Materials and methods

2.1. Subjects

Twenty-four experimentally-naïve adult (>90 days old) female Wistar (Harlan-Sprague Dawley, Madison, WI) rats weighing approximately 250 g were used in the present study. All 24 rats completed a 21-day escalation phase; however, 6 rats (1 HiI and 5 LoI) did not complete the post-extended access PR dose–response condition due to catheter patency issues. Females were used, as they readily escalate cocaine self-administration under conditions similar to those used in the present study (Larson et al., 2007; Roth and Carroll, 2004). Estrous phase was not controlled for in the present study to extend the generality of the findings to females at any phase of the estrous cycle. In addition, long access to cocaine would have been expected to disrupt cycle phase in some animals, making it difficult to control for phase across animals (see Larson et al., 2007). Prior to the experimental sessions, rats had access to ad libitum food (Purina Laboratory Chow, Purina Mills, Minneapolis, MN) and water, and they were pair-housed in plastic cages. Following a 3-day acclimation period, they continued to have free access to water, but they were food restricted (16 g/day) to maintain them at 85% of their free-feeding body weight. All rodent holding rooms were maintained at 24 °C and at 40–50% humidity under a constant light/dark cycle of 12/12-hour with room lights on at 6:00 am. The experimental protocol (0708A15263) was approved by the University of Minnesota Institutional Animal Care and Use Committee. The experiment was conducted in accordance with the Principles of Laboratory Animal Care (National Research Council, 2003), and all laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care.

2.2. Apparatus

2.2.1. Delay discounting for food

Operant conditioning chambers were used to conduct the delay-discounting task as described previously (Perry et al., 2005). The octogonal chambers contained 2 levers (Coulbourn Instruments, Allentown, NJ) located approximately 2.5 cm above the wire mesh floor, and one set of 3 multi-colored stimulus lights was located above each lever. A houselight (4.76 W) was fixed at the top of the operant chamber, and a food hopper (Coulbourn Instruments, Allentown, NJ) dispensed grain-based 45-mg food pellets (PJA1-0045, Research Diets Inc., New Brunswick, NJ) into a food trough that entered the testing apparatus. A drinking bottle was also accessible from the chamber. Data collection and experimental programming were controlled by MED-PC software (Med Associates, St. Albans, VT) on PCs.

2.2.2. Cocaine self-administration

Operant conditioning chambers used for the cocaine self-administration component of the study have been described previously (Carroll et al., 2001) and were identical to those described above except levers were positioned at opposite ends of the chamber, the pellet feeder was not used, and a recessed food reservoir was accessible through an opening in the chamber adjacent to the chamber entrance. The apparatus was designed to prevent spillage and allow accurate measurement of food intake.

2.3. Drugs

Cocaine HCl was provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC). It was dissolved in a sterile 0.9% saline solution at concentrations of 0.8, 1.6, 3.2, and 6.4 mg cocaine HCl/1 ml saline, and refrigerated. An anticoagulant, heparin (1 ml heparin/200 ml of saline; 190 USP units of heparin/kg), was added to the cocaine solution. The cocaine solution was injected at a volume of 0.025 ml/100 g of body weight following a lever press during the cocaine self-administration procedure, and the duration of each infusion was 1 s/100 g of body weight (the average infusion time was 2.5 s).

3. Procedure

3.1. Delay discounting

Rats were screened for either high or low impulsivity using a delay discounting procedure modified from Perry et al. (2005). Daily sessions began with the illumination of a houselight and consisted of fifteen 4-trial blocks. During each block, rats had access to 2 operant levers that produced either a small-immediate reinforcer (one 45-mg pellet) or a large-delayed reinforcer (three 45-mg pellets) contingent upon a lever press (detailed below). Delay-discounting sessions lasted 2 h or until rats completed 60 trials. During experimental sessions, the

lever associated with the small-immediate or large-delayed reinforcer alternated daily to control for a possible side bias in responding. The first and second trial of each block consisted of a forced choice on each operant lever that was signaled by the illumination of stimulus lights located directly above the corresponding response lever. The third and fourth trials were free choice and were signaled by the illumination of the stimulus lights above both levers. On each trial, a lever press on the response-appropriate lever deactivated the stimulus lights and houselight, resulted in the delivery of the small-immediate or large-delayed reinforcer, and initiated a 60-second intertrial interval during which subsequent responses were not reinforced or counted.

The initial delay to the large reinforcer during free- and forced-choice trials was set at 6 s and was adjusted by 1-second increments during the third trial of each 4-trial block, such that the delay decreased by 1 s for a response on the small-immediate reward lever and increased by 1 s on the large-delayed reward lever following the third and fourth trials. The final delay of the session was then used as the initial delay for the subsequent session the next day in order to maintain the individual's range of delays across sessions, and to reduce variability that might result from the rat attempting to return to the desired mean adjusted delay (MAD) during the first several trials of the session. Additionally, following each session, a MAD was calculated by averaging the delays during the 30 free-choice trials, and this was used as quantitative measure of impulsivity. This procedure continued until MAD values stabilized (varying no more than 5 s for 4 days with no increasing or decreasing trend). Rats with MAD values $\leq$6 s were classified as HiI ($n=12$) and those with MADs $\geq$13 s were considered LoI ($n=12$). Rats were supplemented after each discounting session in order to maintain the daily 16 g food allotment.

3.2. Surgery

Following impulsivity screening, rats were anesthetized with ketamine (60 mg/kg) and xylazine (10 mg/kg) and given doxapram (5 mg/kg) and atropine (0.15 ml). A chronic indwelling polyurethane catheter (MRE-040, Braintree Scientific Inc., Braintree, MA) was implanted in the rat's right jugular vein following methods previously outlined by Carroll and Boe (1982), and the rats were housed in an operant chamber where they remained for the duration of the study. Catheter patency was assessed about every 5–7 days by the administration of a 0.1 ml solution containing ketamine (60 mg/kg), midazolam (3 mg/kg), and saline, and a second catheter was implanted in the left jugular vein if a loss of the righting reflex was not manifest during the catheter patency check.

3.3. Cocaine self-administration

Following a 3-day recovery period, rats were trained to self-administer cocaine (0.8 mg/kg) under a FR 1 schedule of reinforcement during daily 6-h sessions. Sessions began with the illumination of the house light at 9:00 am and ended when the light was extinguished at 3:00 pm. During sessions, a response on the left (active) lever resulted in a cocaine infusion and the illumination of a set of stimulus lights located above it. If a rat made a response during an infusion the response was recorded but had no programmed consequences. Responses on the right (inactive) lever resulted in the illumination of the stimulus lights for the duration of an infusion, but they did not activate the infusion pump. Responses on the inactive lever were considered a measure of nonspecific lever pressing, and responses on both levers were recorded. During training, rats received 9 experimenter-delivered priming infusions of cocaine (0.8 mg/kg); 3 infusions at 9:00 am, 11:00 am, and 1:00 pm.

Once rats acquired stable cocaine self-administration (no increasing or decreasing trend in infusions, at least 30 infusions earned for three consecutive days, and a 2:1 active: inactive lever response ratio), priming infusions were discontinued, and the cocaine dose was changed to 0.4 mg/kg. Initial work (Perry et al., 2008) suggested that this training procedure (6-h session, 0.8 mg/kg cocaine) decreased the amount of time needed to reach a steady rate of cocaine self-administration in HiI and LoI rats relative to a standard autoshaping procedure using a smaller dose of cocaine (0.2 mg/kg) (Perry et al., 2005). Following training, rats were allowed to self-administer cocaine for 2-h short access (FR 1) sessions over a 3-day period. Following the third stable post-training day, responding was assessed under the PR schedule for each of 3 doses of cocaine (0.2, 0.8, and 3.2 mg/kg) in random order. Given the difficulty in maintaining catheter life over this extended procedure, two daily sessions (9:00–11:00 am and 1:00–3:00 pm) were used to facilitate rapid stability under the PR condition. The PR schedule used in the present study was similar to that described by Roberts et al. (1989). In this schedule the response requirements for each successive infusion during a single self-administration session were: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, etc. This procedure was used, as previous work from our lab indicated that it was sensitive to group differences in female rats (Larson et al., 2007).

After the rats reached stability at each dose of cocaine with 3 consecutive sessions during which the number of infusions did not differ more than 1 with no increasing or decreasing trends, the dose was changed. Following the PR testing, the cocaine dose was changed back to 0.4 mg/kg, and the session length was extended to 6 h for 21 days (extended access). After the 21-day extended access phase, responses and infusions under the FR 1 short access and PR dose–response conditions were reassessed. Table 1 summarizes the sequence of experimental events.

3.4. Data analysis

Active and inactive responses and infusions during the short-access conditions were analyzed using a 2-factor mixed ANOVA with HiI vs. LoI groups as the between-subjects factor and testing condition (short access before and after extended access) as the repeated measure. Total active and inactive responses and infusions earned under 6 h extended-access sessions and during the first 2 h of extended access were averaged across seven 3-session intervals and compared between the HiI and LoI groups using a 2-factor mixed ANOVA with group as the between-subjects factor and session interval as the repeated measure. A 3-factor mixed ANOVA with HiI vs. LoI groups as the between-subjects factor and cocaine dose (0.2, 0.8, 3.2 mg/kg) and testing condition (pre- vs post-extended access) as the 2 repeated measures was used to compare responses and infusions for 3 doses of cocaine self-administered under the PR schedule before and after extended access. One HiI and 5 LoI rats were excluded from the PR analysis, as their catheters lost patency during the post-extended access PR condition. After a significant interaction, post-hoc tests were conducted using Fisher's LSD protected *t*-tests. MAD values, number of days to MAD stability, number of days to acquisition of cocaine self-administration, and number of infusions self-administered during acquisition were analyzed using two-tailed *t*-tests. All statistical

Table 1
Summary of experimental procedures.

Days	Procedure	Schedule	Cocaine dose (mg/kg)	Session duration
~25	Delay discounting	FR 1	N/A	2 h or 60 trials
~12	S-A training	FR 1	0.8	6 h
3	Short access	FR 1	0.4	2 h
~15	Dose response	PR	0.2, 0.8, 3.2	2, 2 h
21	Extended access	FR 1	0.4	6 h
3	Short access	FR 1	0.4	2 h
~15	Dose response	PR	0.2, 0.8, 3.2	2, 2 h

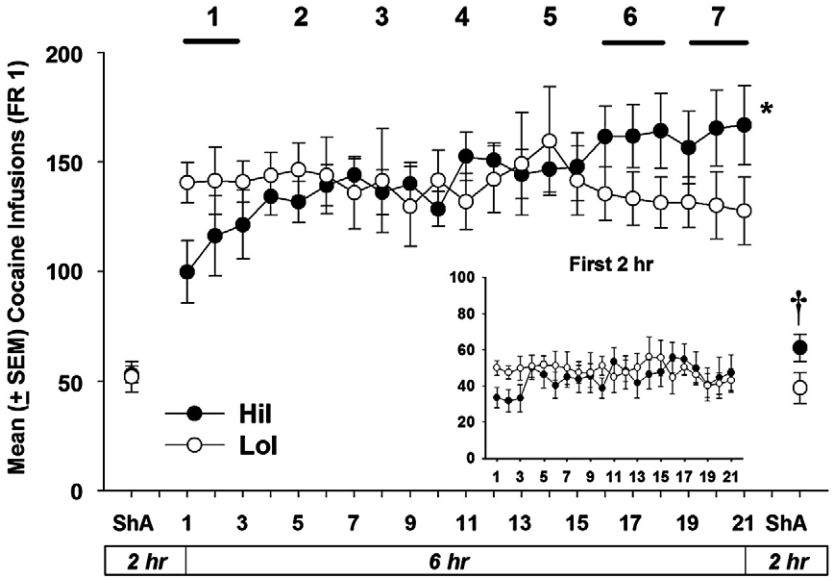

Fig. 1. Mean (±SEM) cocaine infusions (0.4 mg/kg) are presented for each day of the extended access phase (6 h) and for the last day of the short-access (ShA) condition (2 h) before extended access (left unconnected points) and the first day of ShA after extended access (right, unconnected points). The inset represents mean cocaine infusions earned during the first 2 h of extended access. Horizontal lines indicate the 3-day intervals during which there were significant group differences in responses or drug deliveries ($ps<0.05$). During interval 1 (days 1–3) LoI rats earned more cocaine infusions than HiI rats ($ps<0.05$). During interval 7 (days 19–21) the HiI group earned more infusions than the LoI group ($ps<0.05$). HiI (vs LoI) rats also earned more infusions during interval 6 (days 15–18). * = $p<0.05$ interval 1 < intervals 3–7 in the HiI group. † = $p<0.05$ ShA before vs. after extended access in the HiI group and HiI > LoI in ShA infusions after extended access ($p<0.05$).

analyses were conducted using SPSS 16.0 (Chicago, IL, USA). Results were considered statistically significant if $p<0.05$.

4. Results

4.1. Delay discounting for food

Mean (±SEM) MAD values for the HiI and LoI groups were 5.24 (±0.54) and 20.59 (±4.21), respectively ($p<0.05$). There were no group differences in the mean number of sessions to reach stable MAD values on the adjusting delay task [HiI = 26 (±3.7) vs LoI = 29 (±11.9) days].

4.2. Cocaine self-administration

4.2.1. Acquisition

The mean (±SEM) number of sessions for HiI and LoI groups to reach acquisition criteria was 10.7 (±1.44) and 15.83 (±2.49), respectively; however, they did not differ on a *t*-test. There were no group differences in the number of 0.8 mg/kg cocaine infusions earned during acquisition (HiI = 59.32 (±8.38) vs LoI = 69.45 (±4.01) infusions).

4.2.2. Extended-access condition

Fig. 1 shows the mean number of cocaine (0.4 mg/kg) infusions self-administered by HiI and LoI rats during 6-h extended-access sessions and during the 2-h short-access (FR 1) sessions before and after extended access. Infusions earned during the first 2 h of extended access are also displayed (inset). There was a significant HiI/LoI group by session interval interaction ($F_{6, 132} = 2.763$, $p<0.05$) for total infusions during the 6-hour extended-access sessions, but there was not a main effect of either group or session block. Post-hoc analyses revealed that during the first 3 days of extended access, LoI rats self-administered significantly more cocaine than HiI rats ($p<0.05$). However, during the last two 3-day blocks (sessions 17–21), HiI rats earned more infusions than LoI rats ($ps<0.05$). HiI rats showed significant increases in cocaine intake during extended access, earning more infusions during the last 5 intervals (sessions 7–21) compared to the first session interval (sessions 1–3) ($ps<0.05$). In contrast, LoI rats maintained a steady rate of cocaine self-administration during

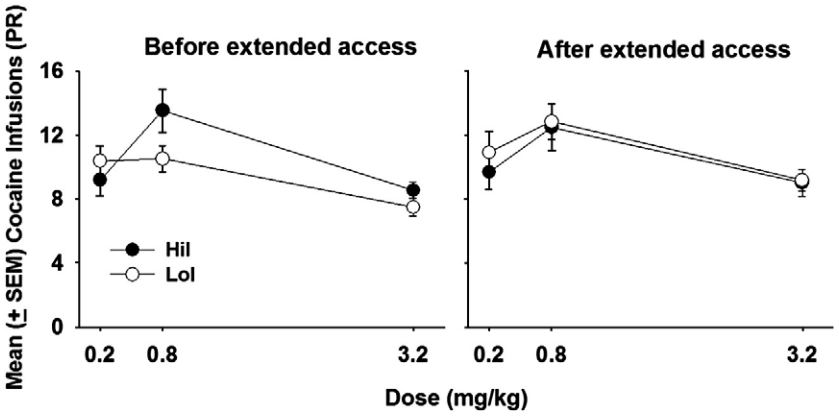

Fig. 2. Mean (±SEM) number of cocaine infusions earned by HiI and LoI rats under a PR schedule before (left panel) and after (right panel) extended access.

extended access. Thus, individual differences in impulsive choice were related to differences in cocaine infusions and their escalation over 21 days of extended access. Similar findings were observed for total reinforced responses on the active lever during extended- and short-access sessions. There were no significant effects or interactions for cocaine infusions or reinforced and nonreinforced responses during the first 2 h of extended access.

A repeated measures ANOVA revealed a significant main effect of the short-access condition before and after extended access ($F_{1,\ 22} = 4.65$, $p<0.05$) and a condition by group interaction ($F_{1,\ 22} = 5.67$, $p<0.05$). The HiI, but not LoI rats, showed significant increases in the number of cocaine infusions following extended access ($p<0.05$). HiI rats also earned significantly more short-access infusions than LoI rats under the post extended-access condition ($p<0.05$). Active and inactive lever presses did not significantly differ between HiI and LoI rats under the short-access conditions.

4.2.3. PR pre- and post-long access

Fig. 2 depicts the mean number of cocaine infusions (0.2, 0.8, and 3.2 mg/kg/infusion) self-administered under the PR schedule by HiI and LoI rats before (left panel) and after (right panel) extended access to cocaine. There was a significant main effect of dose for active ($F_{2,\ 113} = 3.57$, $p<0.05$) and inactive ($F_{2,\ 113} = 17.23$, $p<0.001$) lever responses and infusions ($F_{2,\ 113} = 23.01$, $p<0.001$), but there were no group or condition (pre- vs. post-extended access) main effects nor any interactions among these measures. The number of nonreinforced active and inactive responses did not significantly differ between HiI/LoI groups, doses, or conditions under the PR schedule. Examination of infusions for hours 1 and 2 of each PR session indicated that 80% of infusions occurred in the first hour of testing for the 0.2 and 0.8 mg/kg doses for both groups. However, at the 3.2 mg/kg dose infusions for both groups were spread more evenly across each session with 65% occurring during the first hour.

5. Discussion

The present findings indicate that group differences in impulsive choice predicted the escalation of cocaine self-administration and the persistence of elevated responding under a short-access condition. Similar results were also reported by Dalley et al. (2007) who showed that HiI (vs LoI) rats (on a 5-CSRT task) had a greater tendency to escalate cocaine intake when session length was extended from 5 to 8 h. Thus, heightened impulsivity on two different measures, impulsive choice (delay discounting, present study) and impaired inhibition (5-CSRT, Dalley et al., 2007), were associated with greater escalation of cocaine self-administration in rats. Similar results have been found in human populations. For example, self-reported impulsivity was a significant risk factor in the occurrence of binge-like patterns of crack/cocaine intake in women (Lejuez et al., 2007). Taken together, these results support the hypothesis that impulsivity predicts binge-like patterns of drug intake that typify a critical stage of the addiction process.

HiI and LoI rats displayed opposite patterns of cocaine intake during extended access. LoI rats retained stable levels of cocaine intake across extended access, while HiI rats escalated cocaine intake. One explanation may be that HiI rats were more sensitive to the effects of cocaine under extended access, and this may have resulted in increased cocaine over subsequent days of testing. Similar results using a different impulsivity procedure have been reported by Dalley et al. (2007). In this study, rats designated as high impulsive on a 5CSRT subsequently escalated cocaine intake under an extended-access condition, while rats designated as low impulsive maintained stable levels of intake. These findings indicate that impulsivity under these tasks predicted binge-like patterns of cocaine intake and they suggest that the two impulisivity measures may be related. Indeed, Robinson and colleagues (2009) showed that performance on the 5-CSRT and delay-discounting tasks were correlated.

HiI, but not LoI rats, significantly increased short-access cocaine self-administration following extended access. Group differences in tolerance to the rewarding effects of cocaine (i.e., hedonic tolerance) may have contributed to this elevation, as tolerance following repeated drug exposure resulted in increased cocaine self-administration in animals (Ahmed et al., 2002; Koob and Le Moal, 2001) and humans (Gawin and Kleber, 1988). However, the PR data failed to support this, as cocaine intake before and after extended access was similar between both groups. Heightened short-access intake following extended access may have been dependent on behavior during extended access. For example, increased intake during short access was found only in the groups that had previously shown significant increases in cocaine (Larson et al., 2007) or methamphetamine (Roth and Carroll, 2004) self-administration during extended access. This increase was not present in groups with either very little or erratic increases in cocaine self-administration (Larson et al., 2007; Perry et al., 2006; Roth and Carroll, 2004). Similar to a previous study (Liu et al., 2005), extended access to cocaine self-administration failed to alter PR performance from pre- to post-extended access. These results also support previous work in which rats initially trained to self-administer high (vs. low) doses of cocaine subsequently reached lower breakpoints (final ratio of responses/infusion completed during a single session) under a PR schedule (Morgan et al., 2006). Thus, in the present study, the high training dose of cocaine (0.8 mg/kg) and heightened cocaine intake during extended access may have produced a ceiling effect that obscured group differences during the subsequent PR testing.

The present results are also consistent with previous findings showing greater vulnerability to drug-seeking behavior during other phases of the addiction process. For example, female HiI rats acquired cocaine self-administration more rapidly and in a greater percentage than LoI rats (Perry et al., 2005), and this was later extended to males (Perry et al., 2008). HiI female rats also showed greater drug-induced reinstatement of extinguished cocaine-reinforced responding than LoI females (Perry et al., 2006). Due to the interest of catheter patency and that we were primarily comparing HiI and LoI rats on the escalation of cocaine self-administration, we used a procedure that ensured rapid acquisition of cocaine self-administration but did not allow for analysis of acquisition rates.

The HiI and LoI differences in escalation of cocaine intake found in the present study are in agreement with the relationships found in other addiction-prone and -resistant groups, such as high (vs. low) saccharin-consuming rats (Perry et al., 2006), high (vs. low) runners in a running wheel (Larson and Carroll, 2005), females (vs. males) (Roth and Carroll, 2004), and estrogen-treated (vs. progesterone-treated) female rats (Larson et al., 2007). Overall, the groups that showed accelerated acquisition and reinstatement (HiI rats, high saccharin-consuming rats, high runners in a running wheel, female, and estrogen-treated rats) also showed greater escalation of cocaine intake than their lower-performing counterparts (Carroll et al., 2008). Thus, escalation of drug intake, which is one of the major transition states leading to compulsive drug taking (Koob and Le Moal, 2008), is sensitive to individual differences. Studying these individual differences will be important in determining populations that may be at risk to making a transition from low, controlled levels of drug use to increased, out-of-control levels of drug abuse.

Acknowledgements

This research was supported by the National Institute on Drug Abuse, R01 DA 003240-25, K05 015267-07 (MEC) and F31 DA 023301-02 (JJA). The authors would like to thank Nathan Holtz, Emily Kidd, Amy Saykao, Matthew Starr, and Natalie Zlebnik.

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