Published in final edited form as:

Psychopharmacology (Berl). 2008 December ; 201(2): 195–202. doi:10.1007/s00213-008-1265-x.

Individual Differences in Cocaine-Induced Locomotor Activity in Male Sprague-Dawley Rats and their Acquisition of and Motivation to Self-Administer Cocaine

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Abstract

Rationale—Factors that increase an individual’s susceptibility to cocaine dependence remain largely unknown. We have previously shown that adult outbred male Sprague-Dawley rats can be classified as either low or high cocaine responders (LCRs or HCRs, respectively) based on their locomotor activity following administration of a single dose of cocaine (10 mg/kg, i.p.). Further, LCR/HCR classification predicts dopamine transporter function/inhibition, cocaine-induced locomotor sensitization, and cocaine conditioned place preference.

Objectives—The present study assessed LCR/HCR classification and the development of locomotor sensitization on the latency to acquire cocaine self-administration and motivation to self-administer cocaine.

Results—LCRs and HCRs did not differ in their latency to acquire low-dose cocaine self-administration (0.25 mg/kg/infusion over 12 s, fixed ratio 1 schedule of reinforcement). In a follow-up experiment, repeated experimenter-administered injections of cocaine (10 mg/kg, i.p.) resulted in locomotor sensitization for LCRs, but not HCRs; nonetheless, all rats exhibited decreased latency to acquire cocaine self-administration compared to the first experiment. Repeated cocaine pre-exposure and LCR/HCR classification predicted break point when rats responded for cocaine under a progressive ratio schedule of reinforcement (0.25, 0.5, 1.0 mg/kg/infusion; multiple exposure > single exposure, LCR > HCR), but there was no interaction between these variables.

Conclusions—Although LCR/HCR classification did not predict the rate of acquisition of cocaine self-administration under these conditions, LCR rats demonstrated greater responding for cocaine after acquisition (PR). Thus, these findings demonstrate the relevance of using the LCR/HCR model when studying susceptibility to cocaine dependence.

Introduction

There is now a large body of evidence suggesting individual differences in susceptibility to drug dependence. In humans, initial low sensitivity to alcohol correlated with the development of alcohol use disorders (Schuckit 1994; Schuckit et al. 2006). Initial subjective response to cocaine also predicted cocaine abuse in humans. Lambert et al. (2006) found subjects with greater feelings of “liking” and “wanting” following initial cocaine use were more likely to develop higher lifetime cocaine use and to meet criteria for cocaine dependence.

In rodents, individual differences in response to an inescapable novel environment (low or high novelty responders, LRs and HRs, respectively) have been shown to predict differential

psychomotor stimulant responsiveness. Reports of LR/HR differences in acute amphetamine- or cocaine-induced locomotor activity have been inconsistent (Piazza et al. 1989; Pierre and Vezina 1997; Carey et al. 2003; Quertemont et al. 2004). However, the LR/HR classification has been found more reliably to predict the propensity to self-administer psychomotor stimulants. HRs, compared to LRs, more readily acquired amphetamine self-administration (Piazza et al. 1989), displayed greater active lever responding maintained by low-dose amphetamine following amphetamine pre-exposure (Pierre and Vezina 1997), and developed greater escalation of cocaine intake (Mantsch et al. 2001).

Response to novelty did not, however, predict the magnitude of the conditioned rewarding effects of either cocaine or amphetamine (Gong et al. 1996; Erb and Parker 1994) and has not been reported to predict responding on a progressive ratio (PR) schedule of cocaine reinforcement. These results suggest a difference in the ability of this individual difference to predispose to primary, versus conditioned, reinforcing properties of drugs of abuse. Further, because the response to novelty also predicted the rate of acquisition of an operant response to obtain food reinforcement under some conditions, the facilitation of self-administration observed in HRs might reflect a generalized facilitation of learning, rather than a specific facilitation of drug reinforcement processes (Mitchell et al. 2005).

The initial response to cocaine, like the initial response to novelty, can also differentiate rats in terms of their subsequent response to cocaine. For example, adult outbred male Sprague-Dawley rats were classified as either low or high cocaine responders (LCRs or HCRs, respectively) based on the median split of their open-field locomotor activity during the first 30 min after exposure to a single dose of cocaine (10 mg/kg, i.p.) (Sabeti et al. 2002; Sabeti et al. 2003; Gulley et al. 2003; Briegleb et al. 2004; Allen et al. 2007). Because LCRs and HCRs did not differ consistently in their response to an inescapable novel environment (Sabeti et al. 2002; Gulley et al. 2003) this individual difference might reflect neurochemical underpinnings distinct from the LR/HR model of individual differences.

The differences in initial locomotor responsiveness to cocaine in LCRs/HCRs were related to cocaine's inhibition of the dopamine transporter (DAT) (Sabeti et al. 2002), an interaction critical for cocaine's reinforcing and rewarding effects (Ritz et al. 1987; Chen et al. 2006). Using in vivo electrochemistry, cocaine's inhibition of DA clearance by the DAT in both ventral and dorsal striatum was found to be greater in HCRs than in LCRs (Sabeti et al. 2002). Further, 30-min after acute cocaine administration, [3H]DA uptake into dorsal striatal synaptosomes was greater in HCRs than LCRs, but LCRs and HCRs did not differ in cocaine's affinity for the DAT or cocaine brain levels (Briegleb et al. 2004; Gulley et al. 2003). Interestingly, following repeated cocaine administration, LCRs, but not HCRs, developed cocaine-induced locomotor sensitization and were more likely to develop a cocaine conditioned place preference (CPP) (Sabeti et al. 2003; Allen et al. 2007).

Sensitization to the behavioral and neurochemical effects of psychomotor stimulants most often develops after repeated, intermittent drug exposure (but can occur following a single exposure to higher doses, e.g. Post et al. 1992) and involves long-lasting neuroadaptations (Zahniser and Peris 1992). Further, sensitization has been suggested to play a role in the transition from recreational drug use to addiction (Robinson and Berridge 2001; Ferrario et al. 2005; but see Ahmed and Cador 2006). Psychomotor stimulant pre-exposure decreased the latency to acquire cocaine self-administration (Horger et al. 1990; Schenk and Partridge 2000) and increased responding under a PR schedule of cocaine reinforcement (Mendrek et al. 1998; Suto et al. 2002; Suto et al. 2003). These findings suggest that psychomotor stimulant pre-exposure resulted in sensitization to the reinforcing effects of cocaine.

Because repeated cocaine pre-exposure decreased the latency to acquire cocaine self-administration and repeated cocaine resulted in locomotor sensitization in LCRs, but not HCRs, the present study sought to determine whether LCR/HCR classification also predicts the rate of acquisition of cocaine self-administration. Acquisition was assessed in LCRs/HCRs receiving either single or repeated cocaine pre-exposures. In addition, responding under a PR schedule of reinforcement was assessed to determine the extent to which LCR/HCR classification predicts motivation to self-administer cocaine.

Materials and Methods

Animals

Two groups of outbred male Sprague-Dawley rats (first group $n = 25$; second group $n = 32$) weighing between 300 – 320 g were purchased from Harlan Industries (Indianapolis, IN). Rats were housed individually with *ad libitum* access to food and water in an animal care facility at the University of Colorado Denver -Downtown Campus (UCD). Rats were housed on a 12-h light/dark cycle (lights on at 0700 h), and all testing was conducted during the light cycle. All animal care and use procedures were in strict accordance with the NIH *Guide for the Care and Use of Laboratory Animals* and were approved by the UCD Institutional Animal Care and Use Committee.

Locomotor activity

Locomotor activity was recorded using CPP chambers (Med Associates, Inc., St. Albans, VT). Each chamber contained 15 photobeams, spaced approximately 5 cm apart throughout the chamber. Horizontal movement through the chamber was recorded in one-min bins using Med-PC IV software (Med Associates). Rats were placed in the CPP chambers and allowed to habituate for 60 min, during which time baseline activity was recorded. Activity during the entire 60 min habituation period was analyzed; however, locomotor activity during the 30-min period directly preceding cocaine injection was defined as baseline, as previously reported (Sabeti et al. 2003). After 60 min, rats were removed, injected with cocaine (10 mg/kg, i.p.), and returned to the recording chamber for an additional 60 min. Total locomotor activity over the first 30 min after cocaine injection was summed for each rat, and the median split within each of the two groups was used to characterize rats as either LCRs or HCRs according to previously described methods (Sabeti et al. 2002; Sabeti et al. 2003; Gulley et al. 2003; Briegleb et al. 2004; Allen et al. 2007).

One group of rats received repeated once-daily cocaine exposure to assess the role of cocaine-induced sensitization on self-administration. This repeated pre-exposure (RE) group of rats was injected with cocaine (10 mg/kg, i.p.) for an additional four consecutive days after initial LCR/HCR classification. Locomotor activity was recorded on days 1, 3, and 5. Rats were immediately returned to their home cages after injection with cocaine on days 2 and 4.

Catheter construction and placement

Intravenous catheters were constructed in the laboratory and surgically implanted into the jugular vein under ketamine (100 mg/kg, i.m.) and xylazine (10 mg/kg, i.m.) anesthesia using established procedures (Caine et al., 1993; Allen et al., 2007). Rats received acetaminophen in their drinking water (20 mg/ml) for 2 days as a post-surgical analgesic. Rats recovered from surgery for at least 1 week before self-administration training began. Catheters were flushed with 0.3 ml of bacteriostatic 0.9% sodium chloride that contained heparin (16.7 USP Units/ml) both before and after each self-administration session and on alternate days when not tested. Sodium thiopental (10 mg/kg, i.v.) was administered at the conclusion of each set of experiments to verify catheter patency.

Self-administration training

Rats self-administered cocaine during the light cycle in Plexiglas and metal operant conditioning chambers (29 × 24 × 21 cm; Med Associates). Chambers were housed within sound-attenuating cabinets and contained a fluid delivery trough between two retractable levers on the front wall. Stimulus lights were positioned 6 cm above each lever. A tone presentation speaker (Sonalert Tone Generator, 2900 Hz) and a white noise speaker (90 dB) were mounted on the wall opposite the levers 12 cm above the floor. A houselight (100 mA) was mounted 6 cm above the tone speaker, and a computer-controlled syringe pump delivered cocaine infusions. All behavioral events were monitored and controlled by a personal computer using MED-PC for Windows software (Med Associates).

All self-administration sessions (acquisition and PR) began with the extension of the retractable levers, white noise activation, and illumination of the stimulus light on the right side of the chamber. One second after session initiation, a cocaine priming infusion was delivered (0.25 mg/kg/infusion cocaine in a volume of 0.1 ml over 12 s). During this priming infusion and during all subsequent self-administered infusions, the stimulus light over the active lever was turned off and a tone-houselight conditioned stimulus complex was activated for the duration of the infusion.

Acquisition of cocaine self-administration was measured in 2-h sessions over 25 days. Testing was conducted daily except for one day between sessions 1 and 13 and one day between sessions 13 and 25. Responses on the right lever were reinforced with a cocaine infusion (0.25 mg/kg over 12 s) according to a fixed ratio one (FR1) schedule of reinforcement. Responses emitted on the right lever during the 12-s cocaine infusion were recorded separately from reinforced responses. Responses on the left lever were recorded but had no programmed consequence. Acquisition in these experiments was defined as the first of three consecutive sessions during which an average of ≥ 20 active lever responses was produced. Further, this level of responding had to be maintained for the remainder of the experiment.

After the acquisition experiments, 10 single cocaine pre-exposure (SE) and 10 RE rats that had reached acquisition criterion (20/29 eligible rats) were advanced to PR testing. Groups of 10 were chosen due to the length of the PR procedure and number of self-administration chambers. Rats were matched for similar levels of cocaine intake over the acquisition phase, and each group consisted of five LCRs and five HCRs. The PR experiments consisted of two consecutive PR sessions for each dose of cocaine tested (0.25 mg/kg, 0.5 mg/kg, and 1.0 mg/kg). These PR sessions were separated by a single FR1 session during which responding was reinforced with 0.25 mg/kg/infusion of cocaine. Cocaine doses were tested in increasing order. PR sessions were 5 h in duration, and the response requirement increased progressively according to the following schedule: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, and 737 for cocaine infusions 1–25, respectively (Richardson and Roberts 1996). Break point was defined as the last response ratio completed before 1 h without earned reinforcement or the end of 5 h. As with the acquisition experiments, left lever responses were recorded but had no programmed consequences.

Exclusions and exceptions

In total, 14 of the 57 rats used in this study were excluded from final analysis. Four of the 57 rats that completed locomotor testing were not advanced to the self-administration studies; two rats in the SE group died during surgery and two rats in the RE group were not advanced for health concerns. Nine of the 53 rats used in the acquisition phase of the experiment did not complete the study or were excluded from the final data analysis. In the SE group ($n = 23$), three rats had catheters fail before the end of the 25 sessions. One rat met acquisition criterion by session 4, and this value was a formal statistical outlier when compared with the entire SE

group (17 ± 5 sessions). This rat did not advance to testing under the PR schedule of reinforcement. In the RE group ($n=30$), catheter patency failed for four rats and another rat was excluded for health concerns. Finally, one of the 20 rats that subsequently entered the PR study did not complete it due to failed catheter patency.

Thirteen rats in the RE group inadvertently received exposure to 0.5 mg/kg/infusion cocaine during some of their early self-administration sessions. If this exposure affected acquisition, these rats would have been expected to exhibit decreased latency to acquire cocaine self-administration. However, despite this brief and intermittent exposure to the higher dose, the acquisition curve for this group of rats was indistinguishable from that generated for the 12 rats that received 0.25 mg/kg/infusion cocaine for the entire experiment. Consequently, data from these rats were included in acquisition analysis.

Data analysis

All statistical analyses were conducted using SPSS for Windows, version 16.0. Locomotor activity score was defined as total consecutive beam breaks and represents horizontal movement throughout the CPP apparatus. Non-consecutive beam breaks, which may be more likely to monitor stereotypy, were not analyzed. Although the first 30 min post-cocaine was used to classify rats as LCRs/HCRs, cocaine-induced locomotor activity over 60 min post-cocaine in the RE group was analyzed on days 1, 3, and 5 using two-way (classification x day) repeated measures analysis of variance (RMANOVA) to remain consistent with our previous report (Sabeti et al. 2003). When significant main and interaction effects were revealed, tests for within-subjects differences were analyzed with one-way RMANOVA.

Acquisition variables were analyzed using two-way RMANOVA. Classification and pre-exposure condition were treated as independent variables; latency to acquisition criterion (session) was treated as the dependent measure. PR analysis was conducted on the infusions associated with break point using three-way RMANOVA. Classification, pre-exposure condition, and cocaine dose were treated as independent variables; cocaine intake (breakpoint-associated infusions) was treated as the dependent measure. Responding during the second PR session with each cocaine dose was analyzed. When the assumption of sphericity was violated for a particular repeated-measures analysis, as revealed by Mauchly's test statistic, tests of significance were based on the more conservative Huynh-Feldt corrected degrees of freedom. The symbol, α , indicates Huynh-Feldt corrected values throughout the text.

Drugs

The National Institute on Drug Abuse generously provided the (-)-cocaine hydrochloride used in these studies. For locomotor classification and the RE (sensitization) experiment, cocaine was dissolved in saline (0.9% sodium chloride) at a concentration of 10 mg/ml. These injections were administered i.p. in a volume of 1 ml/kg. For self-administration, cocaine was dissolved in saline containing 1.7 USP Units/ml heparin and infused i.v.. To check catheter patency, sodium thiopental (Sigma, St. Louis, MO) was dissolved in saline and administered i.v. at a concentration of 10 mg/kg. Drug weights refer to the salt.

Results

Individual differences in cocaine-induced locomotor activity and locomotor sensitization

Rats in both experimental groups (SE, RE) were first classified as either LCRs or HCRs in response to a single dose of cocaine (10 mg/kg, i.p.; SE median = 614, RE median = 788). Figure 1 shows baseline and initial cocaine-induced locomotor activity scores for individual rats, as well as mean values $\pm$ SEM for LCRs and HCRs in the SE (Fig. 1a) and RE (Fig. 1b) groups. LCRs and HCRs did not differ significantly in their response to the novel environment

(time 0 – 30 min; data not shown) or baseline activity prior to cocaine injection (time 30 – 60 min) in either group (Fig. 1a and 1b).

Following four additional once-daily cocaine injections (10 mg/kg, i.p.), LCRs and HCRs in the RE group no longer differed in their cocaine-induced locomotor activity (Fig. 1c). Two-way RMANOVA of locomotor activity scores revealed a significant main effect of day [$F(2, 60) = 3.8, p = 0.026$], classification [$F(1, 30) = 10.7, p = 0.003$] and a classification x day interaction [$F(2, 60) = 4.8, p = 0.012$]. Subsequent analysis with one-way RMANOVA for LCRs revealed a significant effect of day [$F(2,30) = 11.6, p < 0.001$]. Compared to day 1, LCRs exhibited significantly greater cocaine-induced locomotor activity on days 3 ($p = 0.007$) and 5 ($p < 0.001$). In contrast, one-way RMANOVA for HCRs did not reveal significant differences across days ($p = 0.584$).

Acquisition of cocaine self-administration

Rats given five days of repeated once-daily cocaine exposure (RE) acquired self-administration of this relatively low dose of cocaine (0.25 mg/kg/infusion) with a shorter latency than rats given a single pre-exposure (SE) (Fig. 2a). This was supported by the results of a two-way RMANOVA (classification x pre-exposure), which revealed a significant main effect of pre-exposure condition [$F(1, 28) = 21.1, p < 0.001$], but neither a significant effect of classification nor a classification x pre-exposure interaction when latency to acquisition (session) was entered as the dependent measure (SE: LCR = 17 ± 1 , HCR = 19 ± 1 sessions; RE: LCR = 9 ± 2 , HCR = 9 ± 1 sessions). Inactive lever responding did not differ between LCRs and HCRs in either the SE or RE groups (data not shown).

In the SE group, 68% of rats (13/19) met acquisition criterion by session 25 (Fig. 2b) whereas in the RE group, 64% of rats (16/25) met acquisition criterion by session 15 (Fig. 2b). RE rats that had reached acquisition criterion by session 15 were advanced to PR testing; those that had not were allowed to continue acquisition testing through 25 sessions. Three additional RE rats reached acquisition criterion by session 25, resulting in 76% acquisition (19/25). In the SE group, 72% of LCRs (8/11) and 63% of HCRs (5/8) reached acquisition criterion by session 25 (Fig. 2b). Likewise, in the RE group 67% of LCRs (8/12) and 85% of HCRs (11/13) reached acquisition criteria by session 25 (Fig. 2b). Fisher's exact test did not reveal significant differences in the overall percentage of rats reaching acquisition criterion in any of the groups (LCR, HCR, SE, or RE).

Responding under a PR schedule of cocaine reinforcement

Following acquisition, 10 rats from each of the two experimental groups that had reached acquisition criterion (SE, 10/13; RE, 10/16) were advanced to PR testing. Each group consisted of five LCRs and five HCRs (SE: 5/8 LCRs and 5/5 HCRs; RE: 5/7 LCRs and 5/9 HCRs). One-way ANOVA did not reveal significant differences between these groups on cumulative cocaine intake during the acquisition phase of the experiment ($p = 0.707$; SE: LCR = 88 ± 23 mg, HCR = 53 ± 20 mg; RE: LCR = 68 ± 22 mg, HCR = 81 ± 18 mg).

The mean numbers of break point-associated infusions earned under the PR schedule are presented in Figure 3a for LCRs/HCRs in the SE and RE groups, and in Figure 3b for LCRs and HCRs combined. Analysis with three-way RMANOVA revealed significant main effects for classification [$F(1,15) = 5.27, p = 0.036$], pre-exposure [$F(1,15) = 5.48, p = 0.033$], and dose [$F(1,15) = 45.0, p < 0.001$], but no interactions were revealed. RE rats earned more cocaine infusions at all doses tested under the PR schedule than SE rats, regardless of LCR/HCR classification (Fig. 3a). Similarly, at all doses tested, LCRs self-administered more cocaine under the PR schedule than HCRs, regardless of cocaine pre-exposure condition (Fig. 3a and 3b).

Discussion

In the present study, LCR/HCR classification predicted motivation to respond for cocaine under a PR schedule of reinforcement, with LCRs exhibiting higher break points at all doses of cocaine tested. LCR/HCR classification did not, however, predict rate of acquisition of cocaine self-administration under a FR1 schedule reinforcement, percent of rats to acquire self-administration, or differences in cocaine intake. Compared to single pre-exposure to cocaine, repeated pre-exposure resulted in locomotor sensitization in LCR rats only, facilitated acquisition of cocaine self-administration (FR1) in both LCRs and HCRs, and increased break point for cocaine under the PR schedule of reinforcement irrespective of LCR/HCR classification.

Individual differences in response to inescapable novelty (LRs/HRs) have been shown to predict acquisition of amphetamine self-administration (Piazza et al. 1989) and escalation of cocaine consumption (Mantsch et al. 2001). However, whether or not the LR/HR classification predicts PR responding for cocaine has not been reported. Here, we found that classifying rats as either LCRs or HCRs did not predict acquisition, but did predict responding on a PR schedule of cocaine reinforcement. Thus, these are novel and distinguishing findings with the LCR/HCR model of individual differences. Increased responding on a PR schedule of reinforcement has been interpreted as indicating increased motivation for drug (Arnold and Roberts 1997), which suggests that LCRs are more motivated than HCRs to self-administer cocaine. One potential caveat for the interpretation of these results is that responding for vehicle under the PR schedule was not measured. However, it is important to note that HCRs reached higher break points for food reinforcement than LCRs (Gulley 2007). These results, together with our current findings, suggest that the differences in PR responding reported here are specific to the motivation to self-administer cocaine, rather than representing more global differences in PR responding between LCRs and HCRs.

In this and our previous studies, LCRs, but not HCRs, developed cocaine-induced locomotor sensitization (Sabeti et al. 2003; Allen et al. 2007). It is important to note that following acute cocaine, HCRs exhibited greater head/limb stereotypies than LCRs (Sabeti et al. 2002). In addition, neither LCRs nor HCRs developed sensitization in head/limb stereotypies following repeated cocaine (Sabeti et al. 2003). Although we did not specifically measure head/limb stereotypies in the present experiments, our previous work suggests that the lack of development of locomotor sensitization in HCRs is not due to sensitization of competing behaviors.

Along with differences in locomotor sensitization, LCRs and HCRs have also been shown to differ on a number of neurochemical measures. Previously, LCR/HCR classification was shown to predict cocaine's inhibition of in vivo DAT activity (i.e., DA clearance; HCR > LCR) within the ventral and dorsal striatum (Sabeti et al. 2002), as well as ex vivo DAT activity in the dorsal striatum (i.e. [³H]DA uptake; HCR > LCR) (Briegleb et al. 2004). Other groups have suggested that cue-controlled cocaine seeking in rats is mediated by the dorsal striatum (Vanderschuren et al. 2005) and that cocaine craving in humans is associated with greater dorsal striatal activation (Volkow et al. 2006). Therefore, given the current finding that LCRs appear to be more motivated than HCRs to self-administer cocaine as indicated by PR performance and previous findings on LCR/HCR differences in DAT function within the striatum, it will be important in the future to assess reinstatement of cocaine seeking in LCRs and HCRs.

One unexpected finding from this study was that cocaine pre-exposure decreased the latency to acquire cocaine self-administration regardless of LCR/HCR classification. Based on the locomotor sensitization differences in LCRs and HCRs (Fig. 1c; Sabeti et al. 2003; Allen et al.

2007) and the finding that sensitization decreased latency to acquire low-dose cocaine self-administration (Horger et al. 1990; Schenk and Partridge 2000), we expected sensitized LCRs to more readily acquire self-administration than non-sensitized HCRs. HCRs still, however, exhibited a decreased latency to acquisition, despite the lack of development of locomotor sensitization. Dissociation between locomotor sensitization and cocaine self-administration has been shown previously (Ahmed and Cador 2006; Lack et al. 2008). For example, rats given extended access to cocaine consumed more cocaine and exhibited greater reinstatement of cocaine seeking behavior than rats given short access to cocaine, but they did not differ in terms of cocaine-induced locomotor sensitization (Ahmed and Cador 2006).

Of note, the present experiments used a relatively low dose of cocaine and a relatively long infusion duration for acquisition training. We chose these conditions to facilitate detection of any potential LCR/HCR differences. Under these conditions cocaine functioned as a reinforcer in ~70% of rats, regardless of pre-exposure condition (68% of SE rats and 76% of RE rats acquired). Dose and infusion speed have been shown to affect both the reinforcing efficacy of cocaine and sensitization to cocaine's reinforcing effects (Liu et al. 2005; Morgan et al. 2006). Therefore, in the future it will be interesting to assess acquisition in LCRs and HCRs over a more extensive range of cocaine doses and/or infusion durations. For example, repeated administration of 1 mg/kg cocaine (i.v.) produces the same differences in locomotor sensitization between LCRs and HCRs as a 10 mg/kg (i.p.) dose (Allen et al. 2007). Therefore, allowing LCRs and HCRs to self-administer higher doses of cocaine (e.g. 0.5 or 1.0 mg/kg/infusion) may reveal differences in acquisition not detected here.

The present study also replicated previous findings of psychomotor stimulant pre-exposure on self-administration. First, this study replicated the finding that repeated cocaine pre-exposure markedly decreases the latency to acquire low dose cocaine self-administration under similar training conditions (Horger et al. 1990; Schenk and Partridge 2000). Second, this study replicated the finding that repeated psychomotor stimulant pre-exposure increases responding on a PR schedule of cocaine reinforcement (Mendrek et al. 1998; Suto et al. 2002; Suto et al. 2003). However, these latter studies used a different training procedure, under which pre-exposure did not appear to alter the rate of acquisition. Regardless, the present study highlights the importance of considering psychomotor stimulant pre-exposure effects when examining the reinforcing effectiveness of cocaine using both FR and PR schedules of reinforcement.

Previous studies have shown individual differences in initial responsiveness to cocaine (LCRs and HCRs) predicted cocaine-regulated DAT function (Sabeti et al. 2002; Gulley et al. 2003; Briegleb et al. 2004), cocaine-induced locomotor sensitization (Sabeti et al. 2003; Allen et al. 2007), and cocaine CPP (Allen et al. 2007). In the present study, we extended this in an important way, by showing that individual differences in initial cocaine-induced locomotor activity predicted motivation to self-administer cocaine. Taken together these findings support the use of the LCR/HCR distinction to examine predisposing factors in cocaine abuse.

Acknowledgments

This work and the authors were supported by NIH grants R37 DA004216, F31 DA023343, T32 GM007635 and K05 DA015050.

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Fig. 1.

Baseline and cocaine-induced (10 mg/kg i.p.) locomotor activity in rats classified as either LCRs or HCRs. Individual baseline (30 min preinjection) and cocaine-induced (30 min postinjection) locomotor activity scores, as well as the mean values $\pm$ SEM over the first 30 min postcocaine, on day 1 are shown for LCRs/HCRs in the SE (**A**) and RE (**B**) groups. The solid horizontal line in panel (**A**) and (**B**) indicates the median. **C** Cocaine-induced locomotor activity (60 min postinjection) in LCRs/HCRs in the RE group is shown on days 1, 3, and 5 of repeated cocaine treatment.

Fig. 2.

Acquisition of cocaine self-administration in LCRs and HCRs. **A** Mean values $\pm$ SEM are shown for active lever responding for cocaine on an FR1 schedule of reinforcement by LCRs and HCRs in the SE (LCR $n=11$; HCR $n=8$) and RE (LCR $n=12$; HCR $n=13$) cocaine preexposure groups during the acquisition experiments. The dashed horizontal line indicates acquisition criterion. **B** Overall percentages of LCRs and HCRs acquiring cocaine self-administration in the SE and RE groups.

Fig. 3.

Cocaine self-administration using a PR schedule of cocaine reinforcement in LCRs and HCRs. Mean values $\pm$ SEM are shown. **A** The number of break point-associated infusions earned on the PR schedule at each cocaine dose tested are shown for LCRs/HCRs in the SE (LCR n=5; HCR n=5) and RE (LCR n=5; HCR n=4) groups. **B** The number of break point-associated infusions earned on the PR for LCRs/HCRs combined across preexposure groups.