Available online at www.sciencedirect.com
ScienceDirect
Pharmacology, Biochemistry and Behavior 85 (2006) 98–104
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Effect of amphetamine on response inhibition in rats showing high or low response to novelty

M.T. Bardo [a,*], M.E. Cain [b], K.E. Bylica [a]

[a] Department of Psychology, University of Kentucky, Lexington, KY 40506, United States
[b] Department of Psychology, Kansas State University, Manhattan, KS 66506, United States

Received 7 September 2005; received in revised form 5 July 2006; accepted 8 July 2006
Available online 14 August 2006

Abstract

Previous work has shown that rats categorized as either high responder (HR) or low responder (LR) based on the amount of activity assessed in a novel environment show a differential response to stimulant reward, with HR rats self-administering more amphetamine and cocaine than LR rats. The current study assessed behavioral inhibitory processes in HR and LR rats using either fixed consecutive number (FCN) or differential reinforcement of low rate of responding (DRL) tasks. Individual differences in free-choice preference for a novel environment or novel object were also assessed to determine if these measures were predictive of performance on these inhibitory tasks. Results showed that, regardless of the test used to characterize individual differences in response to novelty, groups showed a similar ability to learn the FCN and DRL tasks. When subsequently pretreated with amphetamine, there was no significant difference between groups in performance efficiency (accuracy) on either the FCN or DRL task; however, based on activity in inescapable novelty, HR rats were less sensitive than LR rats to amphetamine-disrupted responding on the reinforcement lever in the FCN task. Although a deficit in inhibition is generally thought to play a role in drug abuse behavior, the differential rate of stimulant self-administration described previously between HR and LR rats more likely reflects an incentive motivational effect that is independent of response inhibition.

Keywords: Amphetamine; Novelty; Fixed consecutive number (FCN); Differential reinforcement of low rate of responding (DRL); Individual differences; Drug abuse

1. Introduction

Individual differences in drug abuse vulnerability appear to be related, at least in part, to a personality trait known as sensation seeking or novelty seeking (Donohew et al., 1991; Wills et al., 1998; Zuckerman, 1994). One animal model that has been used most frequently to examine this relationship is the novel "responder" test (Piazza et al., 1989). In this test, rats from a random population are categorized as either high responders (HRs) or low responders (LRs) based on the amount of locomotor activity exhibited in an inescapable novel environment. When tested subsequently for intravenous amphetamine self-administration, HR rats show greater self-administration than LR rats, especially when tested using low unit doses of amphetamine (Klebaur et al., 2001; Piazza et al., 1989; Pierre and Vezina, 1997). One interpretation of these results is that HR rats are more sensitive to the rewarding effect of amphetamine compared to LR rats. However, since HR and LR rats do not differ in amphetamine reward measured by either the conditioned place preference or brain stimulation reward threshold preparations (Antoniou et al., 2004; Klebaur and Bardo, 1999; Robinet et al., 1998), alternative interpretations of the difference obtained with self-administration need to be considered.

Considerable work has indicated that, in addition to differences in incentive motivation to respond for drug reward, individuals may differ in behavioral inhibitory processes. Early work postulated that behavioral output is the net effect of two opposing systems, one that activates behavior via limbic structures and one that inhibits behavior via cortical structures (Gray, 1976). Behavioral inhibition is defined as the ability to withhold a response and a deficit in behavioral inhibition leads

* Corresponding author. Tel.: +1 859 257 6456; fax: +1 859 257 3235.
E-mail address: mbardo@uky.edu (M.T. Bardo).

0091-3057/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2006.07.015

to impulsive behavior. It has been postulated that individual differences in behavioral inhibition may play a role in predicting drug abuse vulnerability (de Wit and Richards, 2004; Fillmore, 2003; Jentsch and Taylor, 1999). In support of this, a recent report found that individual differences in inhibition assessed using a delayed reward discounting task predict subsequent cocaine self-administration in rats (Perry et al., 2005).

The purpose of the present experiments was to assess if HR and LR rats differ in behavioral inhibition in the presence and absence of amphetamine. Amphetamine was chosen based on previous work showing that individual differences predict amphetamine self-administration (Klebaur et al., 2001; Piazza et al., 1989; Pierre and Vezina, 1997). In addition, two different inhibition tasks were chosen, namely the fixed consecutive number (FCN) and differential reinforcement of low rate of responding (DRL) tasks. In the FCN task, rats are required to make a fixed number of responses on one lever and then respond on a second lever for reinforcement. In the DRL task, rats are required to withhold a response for a fixed duration, at which point a single response is reinforced. Both the FCN and DRL tasks are sensitive to the effects of amphetamine (Bayley et al., 1998; Bizot, 1998; Evenden, 1998; Sabol et al., 1995; Wenger and Wright, 1990). In addition to assessing inhibition in rats categorized as HR and LR based on their response to inescapable novelty, the current experiments also assessed inhibition in rats categorized as high or low novelty seekers based on their free-choice preference for either a novel environment or novel object. These latter individual differences were assessed because it has been argued that free-choice access to novelty may be a better model of novelty seeking than the "responder" test that exposes rats to inescapable novelty (Bardo et al., 1996). Both the novel place preference and novel object preference tests have been shown to predict amphetamine conditioned place preference (Klebaur and Bardo, 1999; Robinet et al., 1998).

2. Methods

2.1. Subjects

Adult male, Sprague-Dawley rats (175–200 g body weight) were obtained from Harlan Inc. (Indianapolis, IN), and were housed individually in standard polyurethane cages with free access to food and water, except as noted. The colony room was maintained at 24 °C and 45% humidity, with lights on 07:00–19:00 h. Prior to the start of the experiment, rats were handled and acclimated to the colony for 1 week. Behavioral testing was conducted during the light phase. Procedures were approved by the University of Kentucky Institutional Animal Care and Use Committee and conformed to the 1996 NIH *Guide for the Care and Use of Laboratory Animals*.

2.2. Apparatus

Individual differences in activity in an inescapable novel environment were assessed using a chamber consisting of a rectangular wooden box (24.5×28×43 cm) outfitted with two infrared beams mounted 3 cm above a metal grid floor. The walls were painted white and there was pine bedding under the floor. Beams were oriented at 90° from each other and centered on each wall. Infrared detectors were linked to a personal computer and photobeam interruptions were recorded. A white-noise generator created ambient background noise (~70 dB) to mask sound from outside the chamber. The apparatus was located in an isolated test room with overhead fluorescent illumination.

Individual differences in novel place preference were assessed using a rectangular apparatus that had three different wooden compartments separated by removable solid partitions. The two end compartments measured 28×35×45 cm, and the smaller, middle compartment measured 19×10×45 cm. One end compartment had white walls, a mesh floor, and newspaper beneath the floor. The other end compartment had black walls, a metal rod floor, and pine bedding beneath the floor. The middle compartment had gray walls and a solid wood floor. During testing, the solid partitions were replaced with similar partitions containing a 10×10 cm opening, which allowed the rat access to all three compartments. The apparatus was located in a laboratory room separate from the colony room with a white noise generator and audio speaker (ambient background of ~70 dB). A video camera used to record the experimental sessions was suspended from the ceiling above the apparatus.

Individual differences in novel object preference were assessed using a wooden chamber measuring 63.5×63.5×46 cm that was open at the top. All sides of the chamber and floor were painted gray. The objects used in this test consisted of two identical sand-filled 500-ml brown glass jars with lids and two identical sand-filled Winnie the Pooh plastic drinking cups with lids; each object was approximately 12×6 cm. The rats were not able to move or sit on top of the objects. The objects and apparatus were not cleaned between trials. The apparatus was located in a laboratory room separate from the colony room with a white noise generator and audio speaker (ambient background of ~70 dB). A video camera used to record the experimental sessions was suspended from the ceiling above the apparatus.

Performance on the FCN and DRL tasks was assessed using an operant conditioning chamber (ENV-001, Med Associates St. Albans, VT), which was enclosed in a sound-attenuating compartment and operated by a computer interface. On the front panel of the operant conditioning chamber was a 5×4.2 cm opening that allowed access to a recessed food tray. Two metal response levers were located on either side of the food tray 7.3 cm above a metal-grid floor. A 28 V, 3-cm diameter, white cue light was centered 6 cm above each response lever.

2.3. Procedures

2.3.1. Assessment of individual differences in response to novelty

All rats were screened by one or two "blind" observers in three different novelty tests in the same order: (1) activity in inescapable novelty; (2) novel place preference; and (3) novel object preference. Rats were tested for activity in inescapable

novelty by being placed in the photobeam apparatus for 30 min. Rats were classified into two groups based on a median split of the total photobeam breaks for the 30 min test.

On the following day, each rat began the novel place preference test. Each rat was habituated to either the white or black compartment (counterbalanced) for 30 min/day on each of two consecutive days. On the third day, each rat was tested for novel place preference. Rats were placed in the center gray compartment and were given unrestricted access to all compartments for 15 min. A preference ratio was calculated as the time spent in the novel end compartment divided by the sum of the time in both the familiar and novel end compartments; time spent in the center choice compartment was not included in the preference ratio. Rats were classified into two groups based on a median split of the place preference ratio.

On the following day, each rat began the novel object preference test. Each rat was habituated for 10 min to the novel object testing chamber. On the next day, rats were tested for their preference for a novel object in this apparatus. Two identical objects were placed in adjacent corners of the apparatus, and then the rat was placed in the apparatus facing the wall opposite the objects. The rat was allowed to explore the apparatus with objects for 10 min and then was removed and placed in the home cage. During this time, one of the identical objects was replaced with a novel object. The rat was again placed in the apparatus and the time spent exploring the novel and familiar object was measured for a total of 10 min. A rat was considered to be exploring an object if the nose or front paws were within approximately 2 cm of the object. A preference ratio was calculated as the time spent exploring the novel object divided by the sum of the time spent exploring both the novel and familiar objects. Rats were classified into two groups based on a median split of the novel object preference ratio.

2.3.2. Experiment 1: FCN task

Following assessment of individual differences in response to novelty, food was removed from the home cage one day prior to operant training. On the next day, rats ($n=23$ total) were placed in the operant conditioning chamber and allowed to eat sucrose pellets (45 mg) from the food hopper centered on the front panel (no levers present). On the following day, rats were shaped in one session to press the left lever for sucrose (100 pellets earned) under a continuous schedule of reinforcement; only the left lever was available during shaping. On the following day, rats were similarly shaped in one session to earn 100 pellets on the right lever. Rats were maintained on 15 g of food following each session for the duration of the experiment.

For FCN training, with both levers available during 30-min daily sessions, rats were required to make a minimum number of responses on one lever (FCN lever) before a response on the second lever (reinforcement lever) delivered a reinforcer. Presses on the reinforcement lever prior to completion of the response requirement on the FCN lever resulted in a brief time out, requiring the animal to begin again on the FCN lever. On the first session (FCN 1 schedule), one response on the left lever (FCN lever), followed by one response on the right lever (reinforcement lever), delivered a 45 mg sucrose pellet; lever position was counterbalanced across rats. On the next sessions (FCN 3 schedule), 3 responses on the FCN lever, followed by one response on the reinforcement lever, delivered a sucrose pellet; a response on the reinforcement lever prior to completion of FCN 3 produced a 10-s timeout period during which both cue lights were illuminated. If rats earned at least 45 pellets across 3 consecutive sessions on FCN 3, they were moved to an FCN 8 schedule, in which 8 responses on the FCN lever, followed by one response on the reinforcement lever, delivered a sucrose pellet; a response on the reinforcement lever prior to completion of FCN 8 produced a 10-s timeout period. After 50 sessions, not all rats reached the criterion to move to the FCN 8 schedule. Therefore, at that point, all rats were maintained on an FCN 3 for assessing the effect of amphetamine.

To assess the effect of amphetamine, rats were pretreated 10 min prior to the FCN 3 session with d-amphetamine sulfate (0, 0.1, 0.17, 0.3, 0.56 or 1 mg/kg, s.c.), with the dose order randomized for each rat. Intervening between each amphetamine pretreatment session, rats were given 2 maintenance FCN 3 sessions (no pretreatment) in order to maintain stable responding. The dependent variables were as follows: (1) number of sucrose pellets earned during the session; (2) number of FCN lever presses during the session; (3) number of reinforcement lever presses during the session; and (4) response efficiency, defined by the number of responses on the reinforcement lever divided by the total number of pellets earned.

2.3.3. Experiment 2: DRL task

Following assessment of individual differences in response to novelty, a separate group of rats ($n=24$ total) were reduced to 85% of normal free-feed body weight by restricting food access in the home cage. Rats were then placed in the operant conditioning chamber and allowed to eat sucrose pellets (45 mg) from the food hopper centered on the front panel. On the next day, rats were shaped in one session to press a lever for sucrose under a continuous schedule of reinforcement; only one lever was available during shaping. Rats were then trained for 4 days on a continuous reinforcement schedule in which responding on one lever (active) was followed by a sucrose pellet and responding on the other lever (inactive) had no programmed consequence. Rats were maintained on 15 g of food following each session for the duration of the experiment.

Rats were trained on a DRL 5 s schedule using daily 30-min sessions. On this schedule, each response that was separated from the previous response by a minimum of 5 s was followed by sucrose. Responses which occurred during the 5-s interval reset the timing cycle, but had no additional consequences. The "accuracy" of responding was calculated by dividing the number of reinforced responses by the total number of responses during the session and then multiplying that value by 100 to yield a percentage. Rats were moved to a DRL 10-s schedule if they met the following criteria: (a) 60% or better accuracy for 3 consecutive sessions and (b) less than 10% variability in accuracy over 3 consecutive sessions. Regardless of response stability, all rats were moved to the DRL 10-s schedule after 80 sessions of training.

Once rats achieved stable responding on the DRL 10-s schedule, or after 100 sessions of training, rats received each of 6 different doses of amphetamine (0, 0.1, 0.17, 0.3, 0.56 and 1.0 mg/kg, sc) in random order 10 min prior to the session. Each dose was tested on at least two separate sessions and two maintenance sessions (no pretreatment) intervened between each pretreatment session in order to maintain stable performance on the DRL task.

2.4. Drug

D-Amphetamine sulfate was obtained as a gift from the National Institute on Drug Abuse (supplied by RTI International, Research Triangle Park, NC, USA). Drug was mixed in 0.9% NaCl and injected s.c. in a volume of 1 ml/kg. Doses were based on the salt weight.

2.5. Statistics

Data were analyzed using mixed-factor analyses of variance (ANOVAs), followed by pairwise comparisons using Bonferroni corrected simple effects, a Dunnett's test to evaluate the effect of each drug dose against the single saline control, or planned comparisons. Individual differences based on the 3 different novelty tests were analyzed separately.

3. Results

3.1. Experiment 1: FCN task

The range of scores for the novelty tests were as follows: activity in inescapable novelty (161–613); novel place preference (0.23–0.75); and novel object preference (0.18–0.88). None of the three novelty tests were correlated with one another (all r values were below 0.27; data not shown). Further, separate chi-square tests of independence indicated that novelty classification on each of the three tests were independent of one another. Significance testing for skewness at conservative levels of alpha equal to 0.001 were conducted (Tabachnick and Fidell, 2001) and none of the distribution of scores on the three tests showed significant levels of skewness (z's = −0.038, −1.743, and −0.65 for activity in inescapable novelty, novel place preference and novel object preference tests, respectively), indicating the distributions were essentially normal, as has been illustrated previously in our laboratory (Cain et al., 2005).

Regardless of group classification, there was an overall improvement in performance across sessions in the FCN 3 task. When all rats were included, the initial response efficiency score (mean ± SEM) on sessions 1–5 was 26.8 ± 3.2 and on sessions 51–59 (i.e., the final acquisition sessions prior to evaluating the effect of amphetamine) was 9.4 ± 1.5; among the rats that met criteria (12 out of 24), the initial response efficiency score (mean ± SEM) on sessions 1–5 was 31.1 ± 5.1 and on sessions 51–59 was 6.9 ± 1.7, $t(11) = 4.87$, $p < 0.05$ (two-tailed).

Regardless of the novelty test used, there were no significant differences in the number of rats from each group that met criterion on the FCN 3 task. Based on activity in inescapable novelty, criterion was reached by 8 of 12 HR rats and 4 of 12 LR rats. A chi-square test of independence indicated that there was no significant difference in the number of HR or LR rats to reach criterion. Seven of the HR rats that met criterion were placed on the FCN 8 schedule for a mean of 17 (±4) sessions before being returned to the FCN 3 schedule. Three of the LR rats that met criterion were placed on the FCN 8 schedule for a mean of 22 (±9) sessions before being returned to the FCN 3 schedule. Based on novel place preference, criterion was reached by 5 of 12 rats in the high preference group and 7 of 12 rats in the low preference group; based on novel object preference, criterion was reached by 7 of 12 rats in the high preference group and 5 of 12 rats in the low preference group. Regardless of the novelty test used, chi-square tests of goodness of fit indicated there were no significant differences between groups in the number of sessions to reach criterion on the FCN 3 task. The mean (±SEM) number of sessions required to reach criterion collapsed across group classification was 38 ± 6.

Fig. 1 illustrates the effect of amphetamine on FCN 3 performance in rats classified as HR or LR based on activity in

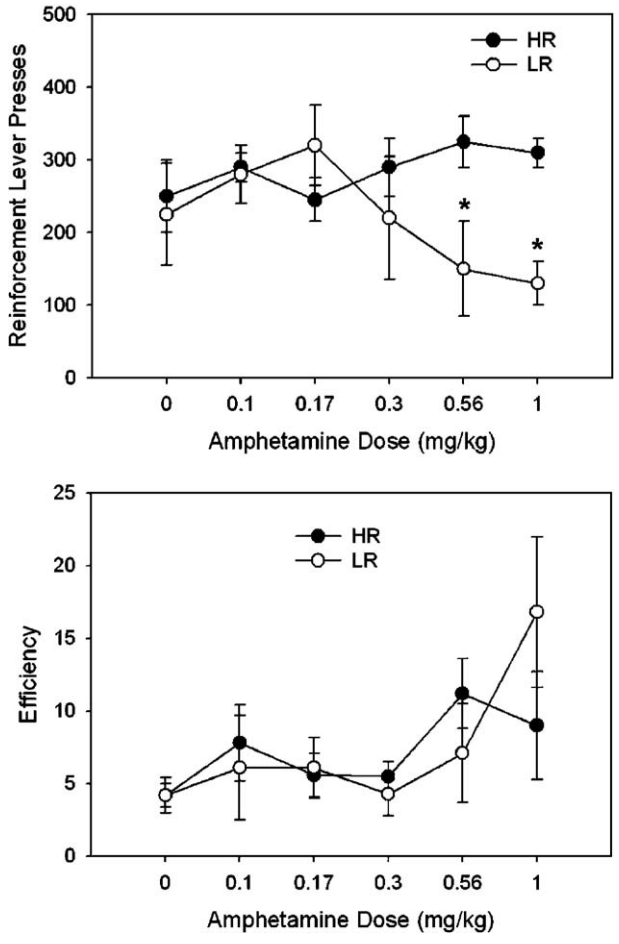

Fig. 1. The effect of varying doses of amphetamine on the mean (±SEM) number of presses on the reinforcement lever (top panel) and the efficiency of responding (bottom panel) on the FCN 3 task in rats classified as HR or LR based on activity in inescapable novelty. Note that lower efficiency scores represent better performance. Asterisk (*) represents a significant difference from HR rats, $p < 0.05$.

inescapable novelty. ANOVA on the number of presses on the reinforcement lever revealed a significant dose × group interaction, $F(5,50)=2.57$, $p<0.05$. Amphetamine disrupted responding on the reinforcement lever in LR rats, but not HR rats (Fig 1, top panel); at the two highest amphetamine doses (0.56 and 1 mg/kg), LR rats showed significantly fewer reinforcement lever presses than HR rats. Amphetamine also increased the response efficiency score, $F(5,50)=2.78$, $p<0.05$, an effect indicative of a decrement in performance; however, no differences between HR and LR rats were evident on this measure (Fig. 1, bottom panel). There were no significant group differences on number of presses on the reinforcement lever or response efficiency when rats were classified into groups based on either the novel place preference or novel object preference tests (results not shown).

3.2. Experiment 2: DRL task

The range of scores for the novelty tests were as follows: activity in inescapable novelty (225–700); novel place preference (0.22–0.82); and novel object preference (0.25–0.87). None of the three novelty tests were correlated with each other (all r values were below 0.28; data not shown). Further, separate chi-square tests of independence indicated that novelty classification on each of the three tests were independent of one another. None of the distribution of scores on the three tests showed significant levels of skewness (z's = 0.034, −0.55, and −0.98 for activity in inescapable novelty, novel place preference and novel object preference tests, respectively), indicating the distributions were essentially normal.

There were no individual differences in acquisition of the DRL 5-s task in rats classified into groups based on activity in inescapable novelty, novel place preference or novel object preference (results not shown). Regardless of group classification, there was an overall increase in accuracy across sessions. The initial accuracy (mean ± SEM) on sessions 1–5 was 55.3 ± 2.5 and on sessions 25–30 was 76.7 ± 1.8, $t(9)=14.08$, $p<0.05$. Shifting rats to the DRL 10-s schedule initially disrupted performance; on sessions 1–5 of the DRL 10-s schedule, the accuracy score was 24.0 ± 1.6 and on sessions 25–30 the accuracy score increased to 54.9 ± 1.5, $t(9)=17.53$, $p<0.05$, indicating acquisition of the more stringent DRL requirement. When stable rates of performance on the DRL 10-s schedule were achieved (sessions 15–30), no significant differences in accuracy scores were evident between groups based on any of the novelty tests. Based on activity in inescapable novelty, HR rats made significantly fewer responses on the inactive lever compared to LR rats, $F(1,104)=31.82$, $p<0.05$, at the end of acquisition training on the DRL 10-s schedule (sessions 25–30; results not shown). However, this difference may not be meaningful since the response rate on the inactive lever was extremely low (mean of 2–6 responses per session, compared to 160+ responses on the active lever).

Fig. 2 illustrates the effect of amphetamine on DRL 10-s performance in rats classified as HR or LR based on activity in inescapable novelty. Regardless of HR or LR classification, amphetamine produced a dose-dependent decrease in active lever presses, $F(5,105)=15.91$, $p<0.05$ (Fig. 2, top panel), although there was no reliable effect of amphetamine on accuracy (Fig. 2, bottom panel). Importantly, there was no significant main effect of group (HR vs. LR) or interaction involving the group factor in the ANOVA for either the number of active lever presses or accuracy. Similarly, no effect of group was evident in separate ANOVAs based on either the novel place preference or novel object preference tests (results not shown).

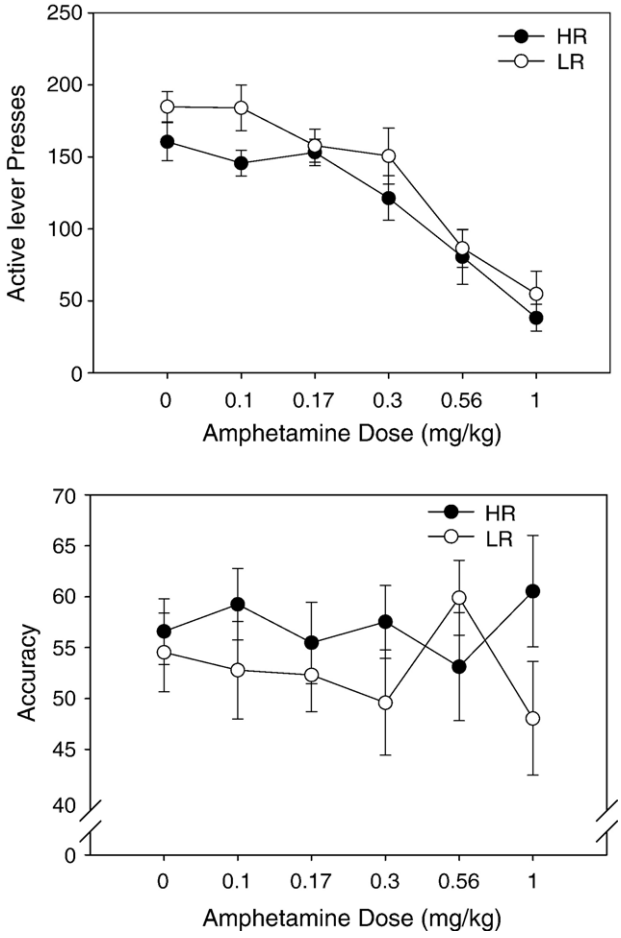

Fig. 2. The effect of varying doses of amphetamine on the mean (±SEM) number of presses on the active lever (top panel) and the accuracy of responding (bottom panel) on the DRL 10-s task in rats classified as HR or LR based on activity in inescapable novelty. Note that higher accuracy scores represent better performance.

4. Discussion

Previous work has shown that when rats are categorized as HR or LR based on the amount of activity in an inescapable novel environment, HR rats acquire and maintain higher rates of amphetamine self-administration compared to LR rats (Klebaur et al., 2001; Piazza et al., 1989; Pierre and Vezina, 1997). However, those previous reports used simple fixed ratio (FR) schedules that tied reinforcement density directly to response rate, and it is not clear whether those results reflect individual differences in reward-relevant activational processes, inhibitory

processes, or both. The current work shows that HR and LR rats acquire at similar rates both a sucrose-reinforced FCN and DRL task, two different procedures that have been used to measure behavioral inhibitory processes. These results indicate that the greater rate of amphetamine self-administration observed previously in HR rats compared to LR rats (Klebaur et al., 2001; Piazza et al., 1989; Pierre and Vezina, 1997) does not reflect individual differences in inhibition, but more likely reflects individual differences in reward-relevant activational systems involving mesolimbic dopamine as described previously (Depue and Collins, 1999). When tested under the influence of varying doses of amphetamine, HR and LR rats also performed with similar efficiency (accuracy) in both tasks. Interestingly, however, HR rats were less sensitive than LR rats to the response disruptive effect of amphetamine on the reinforcement lever in the FCN task. The reduced sensitivity to the rate-decreasing effect of amphetamine in HR rats may offer an explanation for why these animals self-administer more amphetamine than LR rats.

In addition to activity in inescapable novelty, individual differences in the novel place preference and novel object preference tests did not predict acquisition of amphetamine-induced alterations in FCN or DRL performance. While these latter results bolster the conclusion that response to novelty is not associated with inhibitory processes in an operant conditioning situation, a couple of notes of caution are needed. First, previous studies showing that individual differences in these novelty tests predict amphetamine reward have tested rats without food restriction (Klebaur and Bardo, 1999; Klebaur et al., 2001; Piazza et al., 1989; Pierre and Vezina, 1997; Robinet et al., 1998), whereas the current FCN and DRL results were obtained under a food restriction regimen. Second, in the current study, the within-subject design used to test for individual differences in response to novelty and the repeated amphetamine dose regimen could have altered behavior such that the detection of potential individual differences was obscured.

Given that individual differences in response to novelty did not predict FCN or DRL performance, it is important to point out that there are various explanations for changes in performance on these tasks when tested during initial acquisition or under the influence of amphetamine. In general, it is thought that performance on a FCN task depends on the ability to monitor a well-trained behavioral pattern, whereas a DRL task depends on the ability to accurately register the passage of time (Evenden, 1999). Although inhibitory processes influence performance on each of these tasks, it cannot be concluded that the amphetamine-induced decrement in performance is directly attributable to changes in inhibition. Other factors that may explain the amphetamine-induced decrement in FCN and DRL performance include a change in time perception, disruption of short-term memory, attenuation in the punishing effect of nonreward or attenuation in the incentive motivation for sucrose reward. Thus, we cannot rule out the possibility that changes in these other factors may have obscured an underlying difference in inhibition between groups in the current study.

Regardless of group classification based on the different novelty tests, the amphetamine-induced disruption in DRL performance in the present study is consistent with previous work (Wenger and Wright, 1990). However, at least one discrepancy among reports is notable. That is, in contrast to the amphetamine-induced decrease in response rate on the DRL schedule reported in the current study and by Wenger and Wright (1990), other studies have reported that amphetamine may increase response rates on a DRL task (Bizot, 1998; Sabol et al., 1995). The most likely explanation for this discrepancy is that Bizot (1998) and Sabo et al. (1995) used a long duration interval (DRL 30-s or greater), whereas the current study and the study by Wenger and Wright (1990) used a short duration interval (DRL 10-s). These results are consistent with other work showing that the effect of various drugs on DRL performance is schedule dependent (see McClure and McMillan, 1997; McGuire and Seiden, 1980).

Finally, the current results seem somewhat surprising in light of the recent report showing that individual differences in inhibition predict cocaine self-administration in rats (Perry et al., 2005). In that previous work, inhibition was measured using a delay reward discounting task, rather than either a FCN or DRL task as in the current report. Nonetheless, it is notable that individual differences in either inhibition or response to inescapable novelty predict stimulant self-administration (Klebaur et al., 2001; Perry et al., 2005; Piazza et al., 1989; Pierre and Vezina, 1997), even though the current report found that individual differences in inhibition and response to novelty are unrelated. Taken together, these results suggest that inhibition and response to novelty are dissociable phenomena which likely involve separate neurobehavioral mechanisms. This conclusion is consistent with clinical work in personality theory showing that sensation seeking in humans, as measured by the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ) or other related personality instruments (Ball, 2004), is a factor with two distinct traits, one that is activational and one that is inhibitory (Depue and Collins, 1999). Since preclinical models assessing individual differences in drug self-administration have been limited primarily to assessment of single traits, it is important that multiple-trait animal models be utilized in order to gain a more complete understanding of the neurobiological mechanisms associated with individual differences in drug abuse vulnerability.

Acknowledgment

This study is supported by USPHS grants DA 05312 and DA16013.

References

Antoniou K, Papathanasiou G, Panagis G, Nomikos GG, Hyphantis T, Papadopoulou-Daifoti Z. Individual responses to novelty predict qualitative differences in D-amphetamine-induced open field but not reward-related behaviors in rats. Neuroscience 2004;1230:613–23.

Ball SA. Personality traits, disorders, and substance abuse. In: Stelmack RM, editor. On the Psychobiology of Personality. Amsterdam: Elsevier; 2004. p. 203–22.

Bardo MT, Donohew RL, Harrington NG. Psychobiology of novelty seeking and drug seeking behavior. Behav Brain Res 1996;77:23–43.

Bayley PJ, Bentley GD, Dawson GR. The effects of selected antidepressant drugs on timing behaviour in rats. Psychopharmacology 1998;136:114–22.

Bizot JC. Effects of various drugs including organophosphorus compounds (OPC) and therapeutic compounds against OPC on DRL responding. Pharmacol Biochem Behav 1998;59:1069–80.

Cain ME, Saucier DA, Bardo MT. Novelty seeking and drug use: contribution of an animal model. Exp Clin Psychopharmacol 2005;13:367–75.

Depue RA, Collins PF. Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. Behav Brain Sci 1999;22:491–569.

de Wit H, Richards JB. Dual determinants of drug use in humans: reward and impulsivity. In: Bevins RA, Bardo MT, editors. Motivational factors in the etiology of drug abuse. Lincoln, NE: University of Nebraska Press; 2004. p. 19–55.

Donohew RL, Lorch EP, Palmgreen P. Sensation seeking and targeting of televised anti-drug PSAs. In: Donohew L, Sypher H, Bukoski W, editors. Persuasive communication and drug abuse prevention. Hillsdale, CA: Lawrence Erlbaum; 1991. p. 209–26.

Evenden JL. The pharmacology of impulsive behaviour in rats: III. The effects of amphetamine, haloperidol, imipramine, chlordiazepoxide and ethanol on a paced fixed consecutive number schedule. Psychopharmacology 1998; 138:295–304.

Evenden JL. Varieties of impulsivity. Psychopharmacology 1999;146:348–61.

Fillmore MT. Drug abuse as a problem of impaired control: current approaches and findings. Behav Cogn Neurosci Rev 2003;2:179–97.

Gray JA. The behavioral inhibition system: a possible substrate for anxiety. In: Feldman MP, Broadhurst A, editors. Theoretical and experimental bases of the behavior therapies. London: Wiley; 1976. p. 3–41.

Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacology 1999;146:373–90.

Klebaur JE, Bardo MT. Individual differences in novelty seeking on the playground maze predict amphetamine conditioned place preference. Pharmacol Biochem Behav 1999;63:131–6.

Klebaur JE, Bevins RA, Segar TM, Bardo MT. Individual differences in behavioral responses to novelty and amphetamine self-administration in female and male rats. Behav Pharmacol 2001;12:267–75.

McClure GYH, McMillan DE. Effects of drugs on response duration differentiation: VI. Differential effects under different reinforcement of low rates of responding schedules. J Pharmacol Exp Ther 1997;281: 1368–1380.

McGuire PS, Seiden LS. Differential effects of imipramine in rats as a function of DRL schedule value. Pharmacol Biochem Behav 1980;13:691–4.

Perry JL, Lawson EB, German JP, Madden GJ, Carroll ME. Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. Psychopharmacology 2005;178:193–201.

Piazza PV, Deminiere JM, Le Moal M, Simon H. Factors that predict individual vulnerability to amphetamine self-administration. Science 1989;245:1511–3.

Pierre PJ, Vezina P. Predisposition to self-administer amphetamine: the contribution of response to novelty and prior exposure to the drug. Psychopharmacology 1997;129:277–84.

Robinet PM, Rowlett JK, Bardo MT. Individual differences in novelty-induced activity and the rewarding effects of novelty and amphetamine in rats. Behav Processes 1998;44:1–9.

Sabol KE, Richards JB, Layton K, Seiden LS. Amphetamine analogs have differential effects on DRL 36-s schedule performance. Psychopharmacology 1995;121:57–65.

Tabachnick BJ, Fidell LS. Using multivariate statistics. New York, NY: Harper Collins; 2001.

Wenger GR, Wright DW. Behavioral effects of cocaine and its interaction with amphetamine and morphine in rats. Pharmacol Biochem Behav 1990;35: 595–600.

Wills TA, Windle M, Cleary SD. Temperament and novelty seeking in adolescent substance use: convergence of dimensions of temperament with constructs from Cloninger's theory. J Pers Soc Psychol 1998;74:387–406.

Zuckerman M. Behavioral expressions and biosocial bases of sensation seeking. Cambridge, UK: Cambridge Press; 1994.