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ORIGINAL INVESTIGATION

Individual differences in elevated plus-maze exploration predicted progressive-ratio cocaine self-administration break points in Wistar rats

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Abstract
Rationale There are considerable individual differences in vulnerability to drug addiction, but the mechanisms underlying such differences are poorly understood. Cocaine has potent reinforcing effects that support operant responding. However, cocaine also elicits aversive reactions and produces an approach-avoidance conflict in rats. We hypothesized that preexisting individual differences in open arm exploration on the elevated plus-maze, a well-known model for the study of clinically effective anxiolytic drugs, would predict individual differences in cocaine-motivated behavior.
Objectives To assess whether individual differences in sensitivity to anxiety-like behavior on the plus-maze predict motivation to self-administer intravenous (i.v.) cocaine.
Materials and methods Rats were assessed drug-free for individual differences in open arm exploration on the elevated plus-maze, and later trained to perform an operant response for i.v. cocaine (0, 0.1, 0.3, 0.6, 0.9, 1.2, and 1.5 mg kg^{-1} $infusion^{-1}$) on a progressive-ratio reinforcement schedule. Rats were split at the median into low and high open arm explorers based on time spent in the open arms of the plus-maze. Self-administration levels were compared across groups.
Results Rats identified as high open arm explorers on the elevated plus-maze attained higher levels of operant responding for cocaine. Open arm times and break points were significantly correlated at the highest cocaine doses (1.2 and 1.5 mg kg^{-1} $infusion^{-1}$).
Conclusions These results indicate that individual differences in anxiety-like behavior on the elevated plus-maze predict motivation to self-administer cocaine, and suggest the possibility that reduced sensitivity to aversive stimuli may be associated with increased vulnerability to the rewarding properties of cocaine.

Keywords Addiction · Anxiety · Reinforcement · Cocaine · Self-administration · Rat · Operant · Reinforcement

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Not all individuals who are exposed to addictive drugs develop an addiction, and so there is a growing emphasis on research that advances knowledge about predisposing factors for compulsive drug use. Studies with rodents have shown that rats divided into high and low responder groups, based on exploratory activity during forced exposure to a novel environment, show correspondingly high and low levels of psychomotor activity after a systemic injection of amphetamine (Piazza et al. 1989) or cocaine (Hooks et al. 1991). High responders also acquire amphetamine or cocaine self-administration more readily than low responders (Piazza et al. 1989, 2000), and will self-administer higher drug quantities across a range of doses (Piazza et al. 2000). Similarly, rats subdivided into high/low sucrose feeders, based on free-feeding granulated sucrose consumption, show faster and slower acquisition of amphetamine (DeSousa et al. 2000) and cocaine (Gosnell 2000) self-administration. Low sucrose feeders also have a blunted dose-response during maintenance of fixed-ratio amphetamine self-administration (DeSousa et al. 2000), but this was not observed for cocaine

(Gosnell 2000). Overall, these findings indicate that preexisting individual differences in appetitive behaviors can predict sensitivity to the acute behavioral effects of psychostimulants.

However, psychostimulant sensitivity is only one of many factors that could predispose addiction vulnerability. Indeed, a defining feature of this disorder is that drug-seeking persists despite serious consequences for the individual. Accordingly, *insensitivity* to aversive outcomes of drug intake has been proposed as a strong component of addiction-like behavior in rats (Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004). In fact, cocaine itself can produce aversive reactions in humans (Anthony et al. 1989; Geracioti and Post 1991; Walfish et al. 1990) and rodents (DeVries and Pert 1998; Fontana and Commissaris 1989; Rogerio and Takahashi 1992; Yang et al. 1992). Ettenberg and colleagues have demonstrated that approach-avoidance conflict behavior develops in rats given voluntary access to intravenous (i.v.) cocaine. In their model, rats show alternating approach and retreat behavior in close proximity to a goal box where cocaine is delivered (Ettenberg and Geist 1991; Geist and Ettenberg 1990), similar to the behavior that develops when food and foot shock are given simultaneously (Geist and Ettenberg 1997; for review, see Ettenberg 2004). Given these conflicting effects of cocaine, we hypothesized that approach-avoidance conflict sensitivity would predict motivation to self-administer cocaine.

In this study, the elevated plus-maze was used to assess whether the tendency to avoid the aversive open arms would predict individual differences in responding for i.v. cocaine on a progressive-ratio reinforcement schedule. The elevated plus-maze is a well-known assay established by Handley and Mithani (1984) to predict the efficacy of clinically effective anxiolytic drugs. It is designed to assess approach-avoidance conflict behavior by comparing exploration of the open and closed arms. The progressive-ratio reinforcement schedule was established by Hodos (1961) as a way to assess the magnitude or "strength" of a reward. The schedule involves increasing response ratios for each reinforcer until the subject no longer responds, termed the "breaking point." Hodos considered this point to occur when instrumental responding ceased for a 15-min period, but in recent decades the progressive-ratio schedule has been adapted for use in rat self-administration studies by defining it as the point when no drug infusion is earned within 1 h, with response requirements that increase exponentially (Roberts 1989; Richardson and Roberts 1996). In sum, progressive-ratio self-administration provides a response rate-independent assessment of the maximum level of responding that a rat will emit for the drug, and thus measures the drug's reinforcing efficacy more directly than is possible with fixed-ratio schedules.

In our study, we utilized a drug-free exposure to the plus-maze in outbred Wistar rats to measure the association between individual differences in open arm exploration and progressive-ratio cocaine self-administration. We found that higher levels of open arm avoidance on the elevated plus-maze were associated with lower break points for cocaine, particularly at high doses, indicating that animals with lower sensitivity to aversive stimuli may be particularly vulnerable to the reinforcing effects of cocaine.

Materials and methods

Subjects Adult male Wistar rats (Charles River, Canada), weighing 250–275 g upon arrival, were individually housed in Plexiglas® cages within a temperature- (21±1°C) and humidity- (30±5%) controlled colony room on a reversed 12-h light/dark cycle (lights off at 0800 hours). Purina chow pellets and water were freely available in the home cages, except during the initial few days of self-administration training, as described below. Behavioral testing was carried out between 0900 and 1800 hours during the rats' subjective night. All procedures were conducted in accordance with the Guidelines of the Canadian Council on Animal Care and were approved by the University of Toronto Animal Care Committee.

Drugs Cocaine HCl (Bureau of Drug Surveillance, Ottawa, ON, Canada) was dissolved in sterile physiological saline (0.9% NaCl) and loaded into 10 ml syringes before each daily testing session. Cocaine was administered to the rats through the i.v. route in 100 μl infusions delivered over 5.8 s.

Apparatus Operant response training for cocaine self-administration was conducted using 20 fully automatic ventilated operant conditioning chambers, constructed with dimensions of 22 cm^3 with clear Plexiglas® walls, set within a larger sound-attenuating foam-insulated box (Med Associates, Georgia, VT, USA). Within each operant conditioning chamber was an inset food hopper for food pellet delivery, centered along one wall, with a retractable response lever situated on either side of the food hopper. Each lever, when extended, was 4.5×2 cm, mounted 7 cm above the steel rod floor, 5 cm below a white stimulus light. On the wall opposite the levers was a dim house light centered 2 cm below the top of the chamber. Each chamber was equipped with an i.v. liquid swivel infusion assembly attached to an external syringe pump. Two computers equipped with Med PC software for Windows (Med Associates Inc.) allowed for automated session control and data collection from each box.

Surgical procedures Surgeries for catheter implantation followed the sucrose habituation sessions described below. Rats were anesthetized (sodium pentobarbital 60 mg/kg, atropine 0.1 mg), the right jugular was exteriorized and

partially cut, and a Silastic catheter (50±5 μl dead volume) was inserted. The exiting portion of the catheter was reinforced with a polyethylene sleeve and attached to a threaded, stainless steel guide cannula (C313G/Spc, Plastics Products, Roanoke, VA, USA) that was fixed within a dental acrylic base. This assembly emerged from the back at the midscapular region and was secured between the skin and fascia via polypropylene mesh. To maintain patency, catheters were flushed daily with 0.15 ml of saline (0.9% NaCl) containing heparin (50 IU/ml), streptokinase (700 IU/ml), and Penicillin G (250,000 IU/ml) during recovery from surgery (at least 5 days), and with saline containing heparin (30 IU/ml) and streptokinase (200 IU/ml) after recovery. If catheter patency was compromised during the experiment, testing was paused and, if possible, rats were reimplanted with a new catheter into the remaining (left) jugular vein, and again allowed to recover before testing was resumed. Rats that did not complete the cocaine dose-response were removed from the study.

Behavioral procedures

Operant response training Rats were initially trained to perform an operant lever-press response with food reinforcement to accelerate the acquisition of cocaine self-administration. After acclimatization to the housing facilities rats were placed on a restricted food access diet (20–24 g chow/day) to maintain body weight at 85% of free-feeding weight (corrected for growth), and then trained to perform a lever-press response for food pellets (Precision Chow Pellets, PJ Noyes Company, Lancaster, NH, USA) on a fixed-ratio 3 reinforcement schedule during daily 1-h sessions. Once criterion responding was reached (100 pellets with ≥90% accuracy on the active lever), ad libitum food access was resumed before the sugar feeding procedure described below.

Sugar feeding We previously reported that individual differences in sugar consumption predict the acquisition and maintenance of amphetamine self-administration on a continuous reinforcement schedule (DeSousa et al. 2000). We replicated the sucrose feeding procedure in the current study. Rats were habituated to sucrose across eight daily sessions, during which food pellets were removed from the home cage and rats were presented with two preweighed stainless steel cups (8 cm in diameter and 4 cm deep), one filled with granulated sucrose and the other with powdered chow. At the end of the hour food cups were removed and reweighed, and rats were again given ad libitum access to food. After this habituation period, rats were implanted with i.v. catheters as described above, allowed to recover for at least 5 days, and then given a final test for their level of sucrose intake. This testing session was identical to the above habituation sessions, except that rats received a mild stressor (injection of 1 ml/kg, i.p. of saline) immediately before sucrose and chow presentation. This saline injection stress procedure has been used in previously published studies (DeSousa et al. 2000; Sills and Crawley 1996; Sills and Vaccarino 1991), but its importance for separation of high and low sugar consumption groups has not yet been studied systematically. Rats were later sorted based on the mass of sucrose consumed during the test session, and split at the median into high- and low-sugar consumption groups. The median split was used as previously described, and has the advantage of not discarding subjects, and thus maintains sample size (DeSousa et al. 2000; Higgins et al. 1994; Sills and Vaccarino 1991), but we do not presume to use this method to separate rats into two distinct phenotypes, as if the population was bimodal. At this point the characteristics of the population distributions for sugar consumption or elevated plus-maze behavior are poorly understood. Parametric studies of the distribution characteristics using large numbers of subjects would be interesting to pursue in future studies.

Elevated plus-maze Measurement of individual differences in elevated plus-maze behavior involved a single 5-min exposure to the maze (Pellow et al. 1985), given on the day after the test for sugar consumption. The plus-maze was constructed from black, opaque Plexiglas®, and consisted of two opposing open arms (each 10×50 cm with no rims or walls) perpendicular to two opposing closed arms (each 10×50 cm with 40-cm walls), all joined to a center area measuring 10×10 cm. The plus-maze floor was covered with a smooth white plastic material adhered to the surface, and elevated on a center base to a height of 60 cm from the floor of the room. During testing, the room was kept dimly lit and a background of soft white noise was maintained to mask other sounds. Each rat was placed in the middle of the center area facing the open arm opposite from the experimenter, who then left the room while the rat explored the maze. Behavior was videotaped with an overhead camera, and later scored by a researcher blind to the self-administration phase of the study. The maze was thoroughly cleaned with 5% acetic acid and dried between rats. Scoring involved recording the number of entries into each arm, the amount of time spent in each arm, and the center platform. A rat was considered to enter or leave an arm when head and shoulders crossed the boundary between the arm and the center area. Scores for closed arm entries, center time, percent open arm entries, and percent open arm time were recorded for each rat.

Cocaine self-administration training After the above procedures were complete, rats were given access to i.v. cocaine (0.6 mg kg^{-1} $infusion^{-1}$) on a continuous reinforcement schedule during 3-h daily sessions. Each session

commenced with delivery of a 150-μl cocaine priming infusion (100+50 μl dead volume). During this and all subsequent infusions, onset of the infusion was paired with onset of the left stimulus light. The light remained on for 20 s, which coincided with a timeout period during which lever responses were recorded but did not lead to reinforcement. For all rats, operant responses on the left lever (active lever) resulted in i.v. cocaine infusions according to the schedule of reinforcement. Responses on the right lever (inactive lever) were monitored but resulted in no programmed consequences. Continuous reinforcement training sessions were continued daily, for approximately 3 to 4 days, until greater than 90% of lever responses were made on the active lever.

Finally, rats were placed on a progressive-ratio reinforcement schedule after reaching criterion for fixed-ratio cocaine self-administration. The progressive ratio involved escalating response requirements for each subsequent infusion, according to an exponential function described by Richardson and Roberts (1996): response requirement per infusion=$[5e^{(\text{infusion number}\times 0.2)}]-5$ (rounded to the nearest integer). This function yields the following series: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, 737, 901.... Daily sessions were terminated after 1 h passed, during which the rat failed to earn an infusion, with a maximum session length of 5 h. Break points were taken as the number of earned reinforcers in each session, and were evaluated across several cocaine doses (0, 0.1, 0.3, 0.6, 0.9, 1.2, and 1.5 mg kg^{-1} $infusion^{-1}$). Dose order was determined separately for each rat according to a pseudorandomized design, except that for all rats the two lowest doses (0 and 0.1 mg kg^{-1} $infusion^{-1}$) were tested after the higher doses to avoid the possible insertion of extinction sessions into the middle of dose-response testing. Each rat was moved to its next dose after achieving stability over three consecutive sessions. Stability was considered to occur when the standard error of the break points was less than 10% of the mean break point, with no consistent up/down trend in break points observed across three consecutive sessions. The mean break point over the final stable sessions for a given dose served as the score for that dose. Similar calculations were completed for mean interreinforcer intervals, which were calculated as the mean time interval between all earned infusions (excluding the first and last infusions). This can be used as a measure of rate of drug intake (Depoortere et al. 1993).

Statistical analysis Rats were sorted by percent time spent in the open arms of the maze [open arm time/(open+closed arm time)], and split at the median into high open arm explorers ("low anxiety", LAnx) and low open arm explorers ("high anxiety", HAnx) groups. Once the data were separated into LAnx and HAnx groups, *t* tests were used to analyze the compared groups for various behavioral measures taken from the plus-maze. Self-administration behavior was analyzed using a two-way analysis of variance with one between-subjects factor (group) and one repeated measures factor (cocaine dose). Significant interactions were followed up with tests for specific effects of group at each dose. This analysis was repeated for each dependent variable (break point, mean interreinforcer times). In addition, correlation coefficients (Pearson's *r*) were calculated between break points and percent open arm time on the plus-maze at each cocaine dose. Statistica 7.1 (StatSoft) was used for all analyses.

Results

Of the 16 successfully catheterized rats, two of these later developed catheter patency problems before completing the cocaine dose-response, and so were dropped from the study. The cocaine dose-response for the remaining rats showed that break points increased with cocaine dose, but with a gradual flattening of the curve at higher doses. Rate of drug intake increased with cocaine dose in an almost linear fashion. Inactive lever responding was negligible compared to active lever responding for all cocaine doses (Fig. 1). An increase in session length accompanied the higher break points and mean interreinforcer times, but the 5-h limit for the self-administration session was rarely reached—only one rat continued for the full 5 h, and only at the highest cocaine dose tested. With the exception of the 0 mg/kg dose (saline), response accuracy on the active lever remained above 90% at all doses tested.

Behavior on the elevated plus-maze showed substantial variability, with percent open arm time scores ranging from 0 to 87% (median 17.6%), resulting in 48.3±7.7 and 8.2±2.2 (mean±SE) for LAnx and HAnx groups, respectively. Percentages of open arm entries were also higher in the LAnx (45.6±6.1) than the HAnx (22.1±6.3) group ($p<0.05$). Times spent in the center portion of the maze were significantly lower in LAnx (107.1±15.0) vs HAnx (179.7±18.6) groups ($p=0.01$), indicating less hesitation between arms in the LAnx rats. Closed arm entries, an independent measure of general activity, were not significantly different between LAnx (7.3±1.2) and HAnx (7.9±1.2) groups.

Separation of rats into LAnx and HAnx groups revealed an inverse relationship between individual differences in open arm exploration and break points for cocaine. LAnx rats attained to higher break points than HAnx rats across the range of doses, except saline-alone, at which operant response levels were no different between groups (Fig. 2). The group differences were specific for the break point measure and the associated active lever responding because rate of drug intake and inactive lever responding was

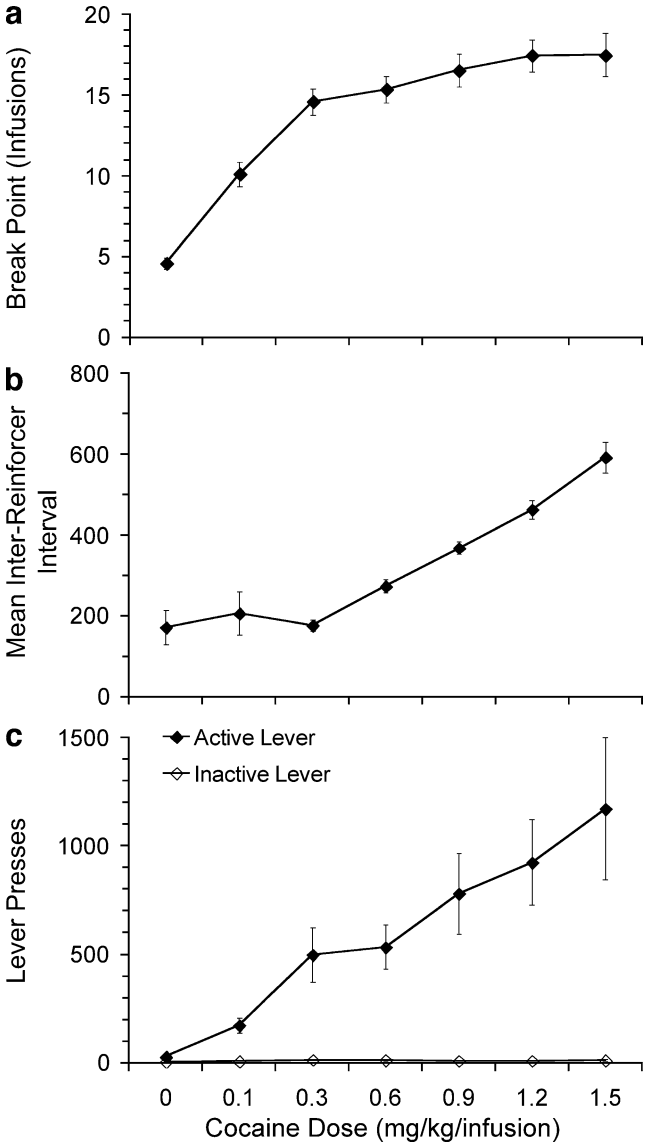

Fig. 1 Dose response for i.v. cocaine self-administration on a progressive-ratio reinforcement schedule depicted for all rats. **a** Break points, shown as total number of earned infusions per session, for each cocaine dose. Data points represent the average break point score for three sessions of stable self-administration at each cocaine dose. Higher break points were associated with higher cocaine doses. **b** Comparison of active and inactive lever presses per session for each cocaine dose. The dose-dependent increase in responding was specific to the active lever. **c** Mean interreinforcer intervals, which indirectly measure the rate of drug intake at each dose, represent the mean of intervals between consecutive drug infusions within each session. Rate of drug intake was slower for higher doses of cocaine

similar for the HAnx and LAnx groups. Unlike individual differences in plus-maze behavior, median splits based on sucrose intake did not predict progressive-ratio cocaine self-administration.

The statistical analysis supported these observations. For break point, there were significant main effects of group ($F_{1,12}$=15.07, p<0.01) and cocaine dose ($F_{6,70}$=58.12, p<0.01). The group × dose interaction was also significant ($F_{6,70}$=2.42, p<0.05), and the analysis of specific effects revealed that LAnx attained to higher break points than HAnx at all cocaine doses except for 0 mg/kg (saline). For mean interreinforcer time, there was a significant main effect of cocaine dose ($F_{6,70}$=35.37, p<0.01), but the main effect of group was not significant. The group × dose interaction was significant ($F_{6,70}$=2.61, p<0.05), but the specific effect of group was significant only at the 0.1 mg/kg dose.

Finally, to further quantify the relationship between plus-maze behavior and progressive-ratio cocaine self-administration, we performed an analysis of the correlation between percent open arm time and break points at each cocaine dose. This analysis revealed a significant positive correlation between percent open arm time and break points at the two highest cocaine doses: 1.2 mg kg^{-1} $infusion^{-1}$ (r=0.61, p< 0.05) and 1.5 mg kg^{-1} $infusion^{-1}$ (r=0.57, p<0.05). Scatter plots with trend lines are shown for these doses (Fig. 3).

Discussion

Cocaine can elicit aversive reactions (Costall et al. 1989; Paine et al. 2002; Rogerio and Takahashi 1992; Yang et al. 1992) that compete with its well-known reinforcing effects (Geist and Ettenberg 1990). Here the elevated plus-maze was used to assay individual differences in conflict behavior among Wistar rats to test the association between open arm avoidance and progressive-ratio cocaine self-administration. The results showed that open arm exploration, assessed in drug-naïve rats, predicted subsequent levels of progressive-ratio cocaine self-administration—low open arm avoiders (LAnx) reached significantly higher break points for cocaine across the full range of doses. This inverse relationship was most evident at highest doses, where the average number of responses for cocaine reached a level that was more than fourfold higher in LAnx vs HAnx rats.

The use of the elevated plus-maze can be traced back to the work of K.C. Montgomery, who described approach-avoidance conflict behavior in rodents exposed to an unprotected alley on the elevated Y-maze (Montgomery 1955). Based on Montgomery's observations, Handley and Mithani later developed the elevated plus-maze as an animal model for the study of anxiety, and validated its usefulness by demonstrating that known anxiolytic and anxiogenic drugs produce an increase and decrease, respectively, in open arm exploration (Handley and Mithani 1984). Since then, the elevated plus-maze has become a widely used tool for studying anxiety-like behavior in rodents. Testing usually involves a single exposure to the maze, is based on spontaneous behavior, has bidirectional sensitivity to anxiety manipulations, and can be used to compare baseline differences in aversion to the open arms (Pellow et al. 1985; Rodgers and Dalvi 1997).

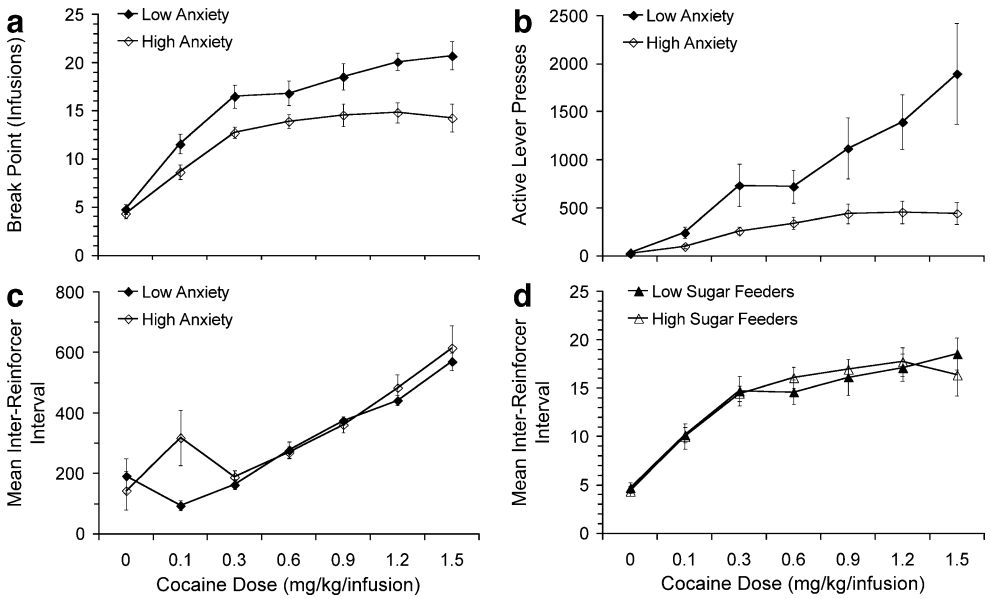

Fig. 2 Comparison of cocaine self-administration behavior in rats that showed high anxiety and low anxiety on the elevated plus-maze. Anxiety was assessed drug-free in rats with no prior exposure to cocaine self-administration. Anxiety groups were divided at the median based on percent time spent on the open arms of the elevated plus-maze. **a** LAnx rats attained significantly higher break points than HAnx rats, evident at all nonzero cocaine doses (*$p<0.05$, **$p<0.01$). **b** LAnx rats showed an approximately linear dose-dependent increase in active lever responses for cocaine, but HAnx rats showed active lever responding that reached a ceiling that was well below maximal responding observed for LAnx rats. **c** Rate of drug intake was similar for LAnx and HAnx rats. **d** Sugar feeding did not predict progressive-ratio cocaine self-administration

In our study, the correlation between plus-maze behavior and progressive-ratio cocaine self-administration suggests that individual differences in these two behavioral settings may be affected by overlapping motivational mechanisms. That is, both cocaine and the elevated plus-maze may present rats with an approach-avoidance conflict. Geist and Ettenberg (1990) have explicitly modeled the conflicting motivational effects of cocaine using a runway task. Rats were trained to traverse a runway and enter a goal box where an i.v. cocaine infusion (0.75 mg/kg) was given. Over repeated trials, rats gradually developed alternating approach and retreat behaviors in proximity to the goal box, indicative of a motivational conflict, similar to the behavioral pattern that developed when rats were simultaneously reinforced with food and foot shock (Geist and Ettenberg 1997). Ettenberg and Geist further characterized the cocaine-induced conflict by showing that retreat behavior is selectively attenuated by pretreatment with anxiolytic drug diazepam. This anticonflict effect of diazepam resembles the decrease in open arm avoidance induced by benzodiazepine agonists on the plus-maze, which was interpreted to indicate that self-administered cocaine has anxiogenic effects (Ettenberg and Geist 1991).

Although these data indicate a clear relationship between plus-maze open arm exploration and progressive-ratio cocaine self-administration, it is important to be cautious about interpreting the current results as evidence for an inverse relationship between anxiety and susceptibility to cocaine reward. The validity of the plus-maze as a tool for measuring trait-like levels of anxiety model has been appropriately questioned (Belzung and Griebel 2001), and the plus-maze behavior was only assessed here using a single exposure. Repeated exposure produces a marked reduction in open arm exploration, possibly because rats learn passive avoidance of the open arms after the first exposure (File and Zangrossi 1993; File 1993; Treit et al. 1993). It will be important for future studies to extend individual differences screening to include additional tests of anxiety. It would also be informative to incorporate other behavioral and physiological measures that can be sampled at multiple time points, such as plasma corticosterone and adrenocorticotropic hormone. Stress hormone responses are of particular interest because Piazza et al. (1991) have implicated corticosterone as a candidate mechanism for individual differences in psychostimulant reinforcement, and have also demonstrated that i.v. corticosterone is self-administered by rats (Piazza et al. 1993; for reviews, see Marinelli and Piazza 2002; Piazza and Le Moal 1997).

We previously reported that high levels of sucrose consumption were associated with higher rates of amphetamine self-administration and more frequent entries into open arms of the plus-maze (DeSousa et al. 1998; 2000). Others have shown that high sucrose consumption predicts greater sucrose- or amphetamine-induced increases in dopamine release within the nucleus accumbens (Sills and Crawley 1996; Sills et al. 1998), suggesting that dopamine

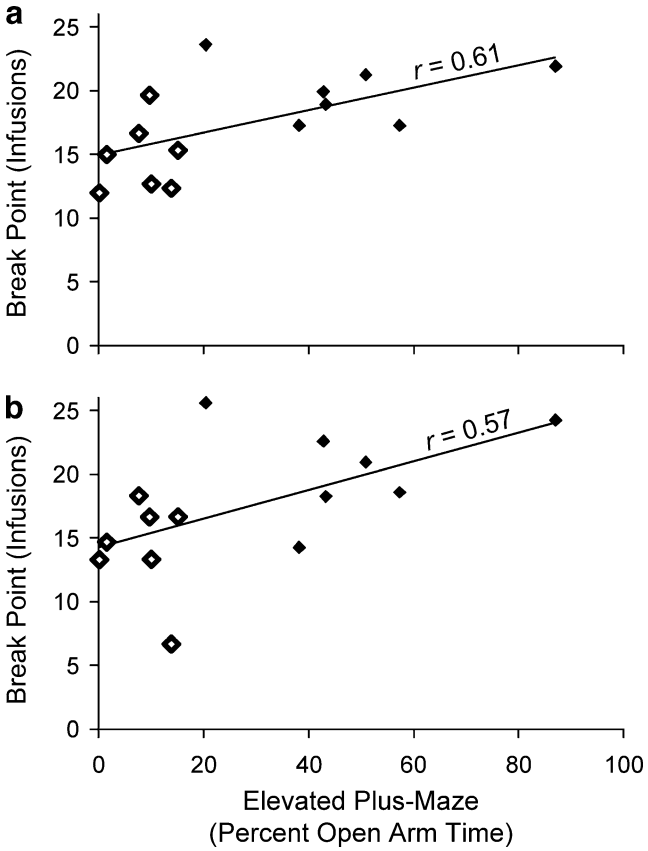

Fig. 3 Percent time spent on the open arms of the elevated plus-maze was significantly ($p<0.05$) correlated with break points for the two highest cocaine doses: **a** 1.2 mg kg^{-1} infusion^{-1} and **b** 1.5 mg kg^{-1} infusion^{-1}. LAnx rats are indicated by *closed symbols*, and HAnx rats by *open symbols*

release may contribute to individual differences in both sucrose- and psychostimulant-motivated behavior. However, the current progressive-ratio results did not support the relationship between sucrose consumption and cocaine self-administration. Distinct reinforcement schedules were used in the two studies, which suggests that sucrose feeding and fixed-ratio drug self-administration may involve overlapping mechanisms that do not contribute to the breaking point. For example, both the sucrose feeding procedure and the continuous reinforcement schedule measure the rate of intake for each reinforcer, whereas the progressive-ratio schedule is considered to be a rate-independent measure of the reinforcing efficacy of each infusion (Richardson and Roberts 1996). Another difference between the studies was that DeSousa et al. (2000) used amphetamine as the drug reinforcer, rather than cocaine. Consistent with this, the Gosnell (2000) study also revealed no association between fixed-ratio cocaine self-administration and sucrose feeding. Further work is needed to investigate whether the reinforcement schedule and/or the drug is a key factor in the relationship between sucrose consumption and psychostimulant self-administration.

The elevated plus-maze has been used to predict aspects of cocaine self-administration behavior in two other studies. Deroche-Gamonet et al. (2004) characterized "addiction-like" behavior in the rat using a rigorous three-dimensional model of drug-motivated behavior in rats with an extensive history of cocaine self-administration. They found an impressive correspondence between epidemiological features of drug addiction in humans (Anthony et al. 1994) and the proportion of rats that showed key aspects of drug addiction. This addiction-like behavior included persistent drug intake despite punishing consequences (insensitivity to punishment), and intense motivation to take the drug (high levels of progressive-ratio self-administration). Plus-maze anxiety did not predict the overall likelihood of addiction-like behavior in their study, but progressive-ratio self-administration responding was only one component of their model. In another study, Homberg et al. (2002) used the elevated plus-maze as a stressor to elicit grooming behavior, and then separated rats into groups of high and low groomers that were subsequently trained to self-administer cocaine. They found that high groomers reached significantly higher break points during progressive-ratio cocaine self-administration. However, because rats were selected from upper and lower quartiles based on grooming, the relationship between open arm exploration and break points for cocaine was not assessed.

Also noteworthy, cocaine self-administration has been shown to be particularly difficult to train in an inbred strain of mice (BALB/cByJ) that is known for high levels of trait emotionality and neophobia. David et al. (2001) successfully trained these mice to nose-poke for low doses of i.v. (0.2 mg kg^{-1} infusion^{-1}) or intraaccumbens (10 ng) cocaine infusions, but the mice gradually extinguished responding, and exhibited retreat behaviors reminiscent of those reported by Ettenberg and Geist (1991). This gradual extinction/suppression of cocaine self-administration was reversed by diazepam pretreatment, and the results were interpreted by the authors to support the hypothesis that cocaine has anxiogenic effects. The results of the present experiment concur with this hypothesis, and combine with those of David et al. (2001) to suggest that individuals with high trait levels of anxiety are more sensitive to cocaine's aversive effects.

Overall, the correlation between plus-maze behavior and cocaine self-administration indicates that individual differences in the sensitivity to the aversive properties of the open arms predict sensitivity to the aversive properties of cocaine. This finding suggests that anxiety could serve as a predictor of individual differences in motivation to respond for cocaine. This, in turn, could provide behavioral screening procedures for a priori collection of physiological and genetic markers of susceptibility to cocaine reward, possibly leading to a more thorough

understanding of factors that put individuals at risk for drug addiction.

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