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Wheel running as a predictor of cocaine self-administration and reinstatement in female rats

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Abstract

Avidity for behaviors mediated by nondrug rewards, such as novelty seeking or intake of sweets or fats, is predictive of enhanced vulnerability to the locomotor-activating and rewarding effects of drugs of abuse. The purpose of the present study was to determine whether avidity for wheel running was predictive of subsequent cocaine-induced locomotor activity, cocaine self-administration, and cocaine-seeking behavior in rats. Rats with high (HiR) and low (LoR) levels of wheel running were selected from an outbred sample of Wistar rats. These rats were first tested for their locomotor response to an acute injection of cocaine (10 mg/kg, i.p.). Subsequently, a multi-phase self-administration procedure was used to examine the effect of wheel running on the maintenance, extinction, and cocaine-induced reinstatement of cocaine-seeking behavior in HiR and LoR rats. The results indicate no significant differences between HiR and LoR rats in the cocaine-induced stimulation of locomotor activity. During maintenance, HiR rats self-administered more cocaine than LoR rats. While there were no group differences in saline self-administration behavior during extinction, HiR rats showed higher cocaine-induced reinstatement than LoR rats. Rats that were previously high responders to novelty (day 1 in locomotor track) also showed significantly higher reinstatement than low novelty responders. These results suggest that a propensity for wheel running is associated with increased vulnerability for cocaine self-administration and reinstatement and that HiR rats are more motivated than LoR rats to seek cocaine.

Keywords: Wheel running; Cocaine; Locomotor; Self-administration; Reinstatement; Relapse; Drug-seeking; Female

1. Introduction

There is evidence that individual differences in drug abuse may reflect individual differences in endogenous characteristics, such as preference for sweets, activity, or novelty-seeking behavior. That is, individuals that strongly express these characteristics are more likely to abuse drugs than those that exhibit low occurrence of these traits (Carroll et al., 2001). In rats, high and low responders (e.g., rats that have high or low expression of a particular trait) can be selected from a population of outbred rats, and these animals can then be assessed on various aspects of drug-mediated behavior. The phenotype of interest can also be exaggerated by selective breeding (Dess et al., 1998). Studies using these methods show that high responders for palatable tastes (Gosnell, 2000; Gosnell and Krahn, 1992; Gosnell et al., 1995; Kampov-Polevoy et al., 1995; Dess et al., 1998; Carroll et al., 2002), novelty-seeking or novelty-induced locomotor activity (Piazza et al., 1989, 1990, 2000; Pierre and Vezina, 1997; Klebaur and Bardo, 1999; Sell et al., 2005), impulsivity (Poulos et al., 1995; Perry et al., 2005), and stress reactivity (Piazza et al., 1991; Piazza and Le Moal, 1996, 1998; Homberg et al., 2002) are more sensitive to the locomotor-activating effects of drugs of abuse, and they are more likely to self-administer drugs compared to their low-responding counterparts.

While increased vulnerability for drug-mediated behavior has been demonstrated in high responders for palatable food, novelty, impulsivity, and stress, the relative vulnerability for drug abuse has not been investigated in rats that are high and low responders for wheel running. Wheel running is a nondrug, noningestive behavior that is actively engaged in by rats, and it

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has reinforcing effects similar to drugs as measured using operant conditioning paradigms. Although it is unknown if there is a "natural" equivalent of wheel running, there is little doubt that it is a particularly rewarding and highly motivated behavior in rats (Sherwin, 1998). For example, rats will lever press for access to running wheels (Iversen, 1993), they show conditioned place preferences for environments associated with the aftereffects of wheel running (Lett et al., 2000), and they escalate their wheel running when given unlimited access to the wheels (Lattanzio and Eikelboom, 2003). Notably, wheel running displays several features that are similar to drug addiction, and these behaviors may have common mechanistic underpinnings. For example, both wheel running and drug self-administration are modified in the same way by the same factors; that is, feeding conditions (Finger, 1951; Carroll, 1985), access duration (Lattanzio and Eikelboom, 2003; Ahmed and Koob, 1998; Ahmed et al., 2000), sex (Hitchcock, 1925; Krasnoff and Weston, 1976; Jones et al., 1990; Lynch and Carroll, 1999; Carroll et al., 2002), and hormonal status (Rodier, 1971; Lynch et al., 2001).

The association between wheel running and the subsequent vulnerability to the reinforcing effects of drugs has been examined in only a few studies. In these, rats with or without wheel access were compared, and it was demonstrated that wheel running experience produced cross-tolerance to the rewarding effects of morphine (Lett et al., 2002). When access was given during ethanol withdrawal, it potentiated subsequent ethanol intake (Werme et al., 2002). However, it is unclear from these studies how individual differences in avidity for wheel running may have influenced subsequent drug-mediated responding. In order to address this issue, in the present study, we compared several measures of cocaine-mediated responding in outbred rats screened for either high (HiR) or low (LoR) voluntary wheel running.

One objective of the present study was to determine whether individual differences in voluntary wheel running predicted the subsequent sensitivity to the locomotor-activating effects of cocaine. Based on previous research with high and low responders for novelty (e.g., Piazza et al., 1989; Sell et al., 2005) or sugar intake (Sills and Vaccarino, 1994), we hypothesized that HiR rats would show greater locomotor activity in response to an acute injection of cocaine compared to LoR rats. A second objective of the present study was to compare HiR and LoR rats on their cocaine self-administration behavior during maintenance, and we predicted that HiR rats would self-administer more cocaine than LoR rats. Currently, the majority of research that has examined the role of individual differences on the vulnerability for drug abuse has focused on self-administration (e.g., during the acquisition phase). However, there is little information about how individual differences can affect drug-seeking behavior during abstinence (Sutton et al., 2000). Therefore, a final aim of the present study was to compare HiR and LoR rats on their cocaine-seeking behavior during extinction and reinstatement, in order to determine whether HiR rats are more motivated than LoR rats to seek cocaine under extended abstinence conditions.

2. Methods

2.1. Animals

Fourteen sexually mature ($\geq$90 days) female Wistar rats (Harlan Sprague Dawley, Madison, WI) weighing 250–340 g were used in this study. Females were used as they are more active in running wheels than males (Hitchcock, 1925; Krasnoff and Weston, 1976; Jones et al., 1990), and HiR/LoR differences were more likely to be detected. Also, there has been little work that has examined factors that predict individual differences mediating drug abuse in females (Klebaur et al., 2001; Sell et al., 2005). While wheel running has been shown to fluctuate across the estrous cycle (Steiner et al., 1982; Kent et al., 1991; Eckel et al., 2000) and can be modulated by gonadal hormones (Rodier, 1971; Morgan and Pfaff, 2002), it was not an aim of the study to examine hormonal regulation of wheel running and its relation to cocaine self-administration and reinstatement. Thus, estrous cycles were allowed to vary randomly and they were not monitored or analyzed.

Rats were acclimated to the lab for at least 3 days prior to surgery, and after surgery they were housed in their experimental chambers for the duration of the experiment. Rats had unlimited access to water and were fed ground Purina Laboratory Chow (Purina Mills, Minneapolis, MN). Food and water were replenished daily starting at 0800 h and intakes were measured and recorded at this time. Rat body weights were measured weekly. Food was available ad libitum *until surgery*. After surgery, it was reduced to 16 g/day and it remained at that amount for the rest of the experiment. We chose to slightly food restrict the rats during self-administration to accelerate training and to control for potential differences in food intake between groups. Using this procedure, food and water intake, as well as rat weights, did not differ significantly during the self-administration, extinction, and reinstatement portions of the experiment (data not shown). Throughout the experiment, all rooms were on a 12/12 light/dark cycle (lights on at 0600 h), and the laboratory was kept at constant temperature (24 °C) and humidity levels. Experimental procedures were approved by the University of Minnesota Institutional Care and Use Committee (IACUC) under protocol number 0112A13581, and laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). Principles of Laboratory Animal Care (National Research Council, 2003) were followed.

2.2. Apparatus

2.2.1. Assessment of locomotor activity

Custom-made circular stainless steel locomotor tracks were used to measure novelty-induced locomotor activity (day 1), baseline locomotor activity (day 2), and locomotor activity after acute exposure to either saline (day 31) or cocaine (day 32). Tracks had inner and outer diameters of 46 and 71 cm, respectively, and the walls were 25 cm high. Tracks were covered with a Plexiglas sheet during testing. Four infrared sensors (SE612CV, Banner Engineering Corp., Minneapolis,