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Rats classified as low or high cocaine locomotor responders: A unique model involving striatal dopamine transporters that predicts cocaine addiction-like behaviors

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Abstract

Individual differences are a hallmark of drug addiction. Here, we describe a rat model based on differential initial responsiveness to low dose cocaine. Despite similar brain cocaine levels, individual outbred Sprague-Dawley rats exhibit markedly different magnitudes of acute cocaine-induced locomotor activity and, thereby, can be classified as low or high cocaine responders (LCRs or HCRs). LCRs and HCRs differ in drug-induced, but not novelty-associated, hyperactivity. LCRs have higher basal numbers of striatal dopamine transporters (DATs) than HCRs and exhibit marginal cocaine inhibition of *in vivo* DAT activity and cocaine-induced increases in extracellular DA. Importantly, lower initial cocaine response predicts greater locomotor sensitization, conditioned place preference and greater motivation to self-administer cocaine following low dose acquisition. Further, outbred Long-Evans rats classified as LCRs, versus HCRs, are more sensitive to cocaine's discriminative stimulus effects. Overall, results to date with the LCR/HCR model underscore the contribution of striatal DATs to individual differences in initial cocaine responsiveness and the value of assessing the influence of initial drug response on subsequent expression of addiction-like behaviors.

Keywords

Individual differences to cocaine; Locomotor activity; Dopamine transporter; Dopamine uptake; Dopamine clearance; NMDAR phosphorylation; Cocaine sensitization; Cocaine conditioned place preference; Cocaine self-administration; Drug discrimination

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1. Introduction

Cocaine is a psychomotor stimulant with high liability for abuse and addiction. Even so, individuals differ widely in their responsiveness to cocaine. Such individual differences are a hallmark of drug abuse and addiction in humans and have been observed in all species tested. Most notably, humans exhibit marked individual variability in susceptibility to cocaine addiction, as evidenced by the estimates that ~15% of all cocaine users develop an addiction (Anthony et al., 1994; Gawin, 1991; Wagner and Anthony, 2002). Part of this differential susceptibility has been linked to individual differences in both subjective and objective responsiveness to the drug. Not surprisingly, individuals who experience positive euphoric effects from their first use of cocaine, compared to those who experience less positive effects or an overt dislike of the drug, are more likely to use cocaine repeatedly (Haertzen et al., 1983). Similarly, college students who had greater positive effect scores when rating their initial drug experience also report greater lifetime cocaine use compared to students with lower positive effect scores (Davidson et al., 1993). In a prospective study, the magnitude of positive subjective responses during initial cocaine use, viz. 'liking' and 'wanting' responses, predicted subsequent cocaine dependence and life-time use (Lambert et al., 2006).

Behavioral activation is characteristic of psychomotor stimulant drugs like cocaine and contributes to the positive subjective responses in humans. In rats, cocaine-induced behavioral activation is revealed by measures such as horizontal locomotor activity, rotational behavior and/or stereotypic motor responses – behaviors that depend upon mesolimbic and nigrostriatal dopamine (DA) neurotransmission. Cocaine blocks all three monoamine transporters – the DA transporter (DAT), serotonin transporter (SERT), and norepinephrine (NE) transporter (NET) – with approximately equal affinities (200–300 nM; Hyttel, 1982). Nevertheless, the locomotor stimulant, rewarding and reinforcing effects of cocaine have all been primarily associated with its blockade of DATs and the resulting elevation in extracellular DA levels in the ventral striatum (i.e., nucleus accumbens; NAc) and dorsal striatum (dSTR), the terminal fields of the mesolimbic and nigrostriatal DA neurons, respectively (Chen et al., 2006; Giros, et al., 1996; Ritz, et al., 1987; Thomsen et al., 2009). Further, brain imaging has demonstrated a direct relationship between the subjective 'high' produced by intravenous (i.v.) cocaine and DAT occupancy by the drug, with a minimal striatal DAT occupation of 47% required for participants to perceive cocaine's subjective effects (Volkow et al, 1997).

Understanding the basis for individual differences in responsiveness to cocaine could help in predicting cocaine abuse liability and in developing more effective prevention and treatment strategies for cocaine abuse and addiction. To this end, over the past decade we have identified and characterized an animal model based on individual differences in initial locomotor response to cocaine. We classify outbred Sprague-Dawley rats as either low or high cocaine responders (LCRs or HCRs, respectively) based on the median split of each group of rats' locomotor activity after an acute intraperitoneal (i.p.) injection of a relatively low dose of cocaine (10 mg/kg). This model has proven useful to study individual differences in addiction-like behaviors concurrently with biochemical measurements. Further, since many labs use outbred Sprague-Dawley rats and assume a more or less consistent response to cocaine among them, we thought that it was important to understand (i) what was responsible for these individual differences and (ii) if these differences could be exploited to provide insights about differential vulnerability to cocaine use and addiction. Here, we discuss the basis for our model, what we have learned with it to date (summarized in Table 1), and why we think this model makes a unique and valuable addition to the other existing animal models of cocaine use and addiction vulnerability.

2. The LCR/HCR model of individual differences to cocaine

2.1 Acute cocaine-induced locomotor activity, stereotyped behaviors and anxiety

The LCR/HCR model developed and studied in our laboratories is based on our longstanding observation that an acute i.p. injection of 10 mg/kg cocaine [(–)-cocaine HCl] results in markedly different magnitudes of behavioral activation among individual rats. Thus, in each group ($n = 12$) of outbred male Sprague-Dawley rats tested, animals consistently exhibit a wide range of cocaine-induced locomotor activation -- from little or no activation to marked activation (Fig. 1a). We have observed this heterogeneity within groups of rats both in early studies when the rats' cocaine-induced locomotor activation was scored manually (e.g., Cass et al., 1993) and more recently with automated open-field chambers (e.g., Sabeti et al., 2002).

In each group of rats studied, we use the median split of the group's horizontal locomotor activity during the first 30 min after the acute cocaine injection to classify rats with activity below the median as LCRs and those with activity above as HCRs (Fig. 1b; Sabeti et al., 2002). Once the rats are classified as LCRs or HCRs, we can also compare novelty-induced (first 30 min; Fig. 1b) and baseline (30 min before injection; Fig. 1b) activity, as well as the locomotor activity during the entire 120-min behavioral monitoring session for LCRs, HCRs, and vehicle (saline) controls (Fig. 1c). Typically, LCR and HCR group means for acute cocaine-induced locomotor activity differ by two- to four-fold, whereas novelty and baseline activity does not differ between LCRs and HCRs. Our findings with the LCR/HCR model are summarized in Table 1. Although we routinely use distance traveled during the 30-min post-cocaine period for classification (Fig. 1b), we have found that the initial 20 min after cocaine (10 mg/kg, i.p.) is the minimum period necessary for defining male Sprague-Dawley rats as either LCRs or HCRs (Mandt and Zahniser, 2010).

Since a great deal of variability in initial response to cocaine exists, it is not surprising that individual differences in initial locomotor response to cocaine are readily observed in both male and female rats, as well as in different rat strains. Similar to male Sprague-Dawley rats, male Long-Evans rats are readily classified as LCRs and HCRs (Gulley, 2007). Likewise, outbred female Sprague-Dawley rats can be divided into LCRs and HCRs (Mandt et al., 2009). In agreement with other studies showing that female rats are more sensitive to cocaine (Festa et al., 2004; Sell et al., 2000; Walker et al., 2001), we found that 5 mg/kg cocaine produces a similar range of locomotor activation as 10 mg/kg cocaine in male rats (Mandt et al., 2009). It should be noted that locomotor activity following a vehicle injection does not differ between LCRs and HCRs (Sabeti et al., 2003). While we have not conducted an exhaustive LCR/HCR cocaine dose-response study in outbred Sprague-Dawley rats, we have classified LCRs and HCRs at 10, 15 and 20 mg/kg doses in males (Gulley et al., 2003; Rorabaugh and Zahniser, unpublished observations) and 5 and 10 mg/kg doses in females (Mandt et al., 2009). We have observed that as the cocaine dose increases, individual differences in locomotor activity and stereotypies decrease, suggesting that relatively low doses are needed for LCR/HCR classification and, further, for determining the molecular underpinnings of their initial differential locomotor responsiveness to cocaine.

Although we classify each group of rats into two discrete phenotypes, we have only occasionally observed a distinctly bimodal distribution for cocaine-induced distance traveled within a group of rats. Most often, the frequency distribution of the individual values is more-or-less continuous but with a flatter, broader spread than a normal Gaussian distribution, as measured by kurtosis (Sabeti et al., 2002). Rather than including all rats in the LCR/HCR model, we could use only the rats with the lowest and highest locomotor responses to cocaine. Several models of individual differences, based on other behaviors, use only the top and bottom thirds or quartiles (Belin et al., 2008; Broos et al., 2012; Flagel

et al., 2008; Gong et al., 1996). By including the animals whose activation levels are close to the median, we are certainly less likely, due to a potential loss in power and introduction of Type 1 error, to find statistical differences between LCRs and HCRs in other associated measures, in particular those that make only a minor contribution to the phenotype. Nonetheless, the continuum of cocaine-induced activation appears to be representative of normal population heterogeneity, and we have found the LCR/HCR classification useful for identifying underlying mechanisms and predicting addiction-like behaviors. This approach allows us to use all of the rats within the group to determine whether or not the individual rats' behavioral and biochemical measures are correlated, regardless of LCR/HCR classification. Correlational analyses, used to follow up on significant LCR/HCR group differences, strengthen arguments about the relationships identified using the two groups defined by the median-split of their cocaine-induced locomotor activity behavior.

Cocaine-induced stereotypic behaviors can compete with locomotor activity. Although competition between stereotypy and locomotor activity likely contributes, it does not fully explain the initial differences in cocaine-induced activation between LCRs and HCRs. Following 10 mg/kg cocaine, LCRs display more freezing behaviors initially; and their movement is largely confined to head movements (bobs or sways) and sniffing (Gulley et al. 2003; Sabeti et al., 2002). In contrast, HCRs, in addition to the increased head movements and sniffing, also display increased exploring and rearing behaviors in the first 60 min post-cocaine. Similar observations hold true for a 20 mg/kg, i.p. initial classification dose, although there is less disparity between groups. On the other hand, self-grooming behavior - sometimes used as a measure of anxiety - does not differ between the groups after cocaine exposure. Likewise, following acute cocaine neither plasma corticosterone levels nor thigmotaxis differ between LCRs and HCRs, consistent with the idea that anxiety does not play a major role in these two phenotypes (Nelson et al., 2010). We also note that there are no LCR/HCR differences in any of the aforementioned behaviors or parameters in the 30 min before cocaine injection.

2.2 Repeated cocaine-induced locomotor activity: Behavioral sensitization

In addition to the differential locomotor response after acute cocaine, Sprague-Dawley rats that are less activated initially (LCRs) more reliably develop locomotor sensitization than HCRs in response to repeated, intermittent cocaine exposure (Allen et al., 2007; Cass et al., 1993; Mandt et al., 2008, 2009; Nelson et al., 2009, 2010; Sabeti et al., 2003; Yamamoto and Zahniser, 2012). Importantly, we have observed similar results administering 10 mg/kg i.p. or 1 mg/kg i.v. cocaine to male Sprague-Dawley rats (Allen et al., 2007). Likewise, male Long-Evans rats classified as LCRs develop behavioral sensitization, but HCRs do not (Klein and Gulley, 2009). To test for sensitization, our usual protocol is to administer the same dose used for classification on day 1 (10 mg/kg, i.p.) for the next 6 days. On days 1, 3, 5, and 7, the rats' locomotor activity is monitored for 90 min before and 30–60 min after an injection of either cocaine or saline (for vehicle controls). On the alternate days rats are given injections in the behavioral testing room, but their locomotor behavior is not monitored. Our criterion for sensitization is the following: locomotor activity in the first 30 min post-cocaine on day 7 must be 2X that on day 1. LCRs develop sensitization over the course of repeated cocaine exposure (3–5 days), until their cocaine-induced activity no longer differs from that of the HCRs (Mandt et al., 2009; Nelson et al., 2009; Sabeti, 2003). With the exception of one study, HCRs have not exhibited locomotor sensitization (Mandt et al., 2009). Sensitization is not manifested in head/limb stereotypies in either LCRs or HCRs or accompanied by differences in plasma corticosterone (Nelson et al., 2010; Sabeti et al., 2003). It has been proposed that locomotor sensitization predicts increased incentive salience, drug craving, and relapse to drug seeking (Robinson and Berridge, 2003; Steketee and Kalivas, 2011). Therefore, in future studies it will be important to test for LCR/HCR

differences in relapse to drug seeking using the behavioral model of reinstatement to self-administration.

2.3 Brain cocaine levels after acute and repeated cocaine

An obvious potential explanation for the differential LCR/HCR cocaine-induced locomotor activation would be markedly higher brain levels of cocaine in HCRs than LCRs. To address this, we measured levels of cocaine in dSTR and NAc of male Sprague-Dawley rats 30 min after acute cocaine (10 mg/kg, i.p.; Gulley et al., 2003). We found no significant differences between LCRs and HCRs in either brain region. Correlation analyses between the individual values for brain cocaine and cocaine-induced distance traveled, regardless of LCR/HCR classification, revealed that the slope of the regression line was not significantly different from zero in dSTR, but was significantly positive ($r^2=0.1766$, $p = 0.03$) in NAc. While this difference in NAc accounted for ~18% of the overall variability and could contribute to the increased locomotor activation in HCRs, it is unlikely that the small magnitude of this difference fully explains the 2- to 4-fold differences in cocaine-induced locomotor activation routinely observed between LCRs and HCRs (Fig. 1b).

More recently, we addressed this question again by measuring cocaine levels in cerebral cortex after both acute and repeated cocaine (10 mg/kg, i.p.). Levels were measured 40 min after acute cocaine or after injection on day 7 of repeated cocaine in the two groups of rats. Similar to the findings of Gulley et al. (2003), we detected no differences in cortical cocaine levels following acute drug administration (Fig. 2a) and no correlation between cocaine-induced locomotor activity and cortical cocaine levels (Fig. 2b). Brain cocaine levels measured in the cortex after repeated cocaine also revealed no LCR/HCR differences (Fig. 2c). As was previously observed, LCRs, but not HCRs, developed locomotor sensitization over the 7-day cocaine treatment. However, again similar to the acute cocaine results, no overall correlation was found between the individual rats' cocaine-induced distance traveled and brain cocaine levels (Fig. 2d). Together, these results suggest that cocaine pharmacokinetics does not play a major role in the LCR and HCR differences in cocaine-induced locomotor responses, nor does it explain the preferential development of locomotor sensitization in LCRs.

3. Other rat models for individual differences

A number of rat models, based on baseline behavioral differences, have been developed and have proven useful for studying specific aspects of cocaine addiction-like behaviors (see Table 2). Only the models with published results most relevant to our results with the LCR/HCR model are presented here. The basis for classifying high responders/low responders (HRs/LRs) is their differing magnitudes of locomotor activity in an inescapable novel environment (Blanchard et al., 2009; Flagel et al., 2010; Hooks et al., 1991; Piazza et al., 1989; Verheij and Cools, 2008). High and low novelty preference rats (HNP and LNP) differ in novelty-induced place preference (Belin et al., 2011; Klebaur et al., 2001). The "sign-tracker" (ST), "goal-tracker" (GT) model is based on Pavlovian learning in which a conditioned stimulus (CS) is paired with an unconditioned stimulus (US), in this case a food reward (Flagel et al., 2008). For STs, the CS, or "sign", develops incentive salience and they approach it before going to the food, whereas GTs approach the food directly. Still other groups have divided rats into high and low impulsivity cohorts (HI and LI) based on the five choice serial reaction time (5-CSRT) task of sustained visual attention or on a delayed-discounting task (Belin et al., 2008; Dalley et al., 2007; Molander et al., 2011; Perry et al., 2005).

Selectively bred rats have also proven to be useful models for psychostimulant studies. These include the Roman high and low avoidance (RHA and RLA) rats, which have been

selectively bred for rapid vs. poor acquisition of two-way active avoidance behavior in a shuttle box (Steimer et al., 1997) and rats bred for high saccharin (HiS) or low saccharin (LoS) intake (Carroll et al., 2008). Selective breeding has also been applied to the HR/LR model, yielding selectively bred rat lines for high and low locomotor response to an inescapable novel environment (bHR/bLR; Stead et al., 2006). These models have been useful for correlating baseline behaviors that may predispose an animal to addiction with behaviors in models of reward and reinforcement, such as conditioned place preference (CPP) and self-administration. However, none of these models base their differences on initial response to drug, or specifically cocaine, which, as was mentioned in the Introduction, has been shown to be predictive of future use and dependence in humans (Davidson et al., 1993; Haertzen et al., 1983; Lambert et al., 2006). Here, we will compare and contrast behavioral results obtained with these other rat models (Table 2) to our findings with LCRs/HCRs (Table 1).

3.1 Novelty-induced locomotor activity

One characteristic of our rat model is that LCRs and HCRs do not differ in locomotor activity in a novel environment before cocaine exposure (Fig. 1b). Further, when we reclassify Sprague-Dawley LCRs/HCRs as LR/HRs, they do not consistently differ in their locomotor response to their initial exposure to cocaine (Gulley et al., 2003). Thus, this not only clearly distinguishes the LCR/HCR model from the LR/HR model but also underscores the necessity of administering cocaine to distinguish between LCRs and HCRs behaviorally. In contrast, as previously mentioned, in an inescapable novel environment HRs are more active than LRs (Piazza et al., 1989). Similarly, novelty-induced locomotor activity in RHA rats is greater than in RLA rats (Steimer et al., 1997); and LoS rats exhibit higher locomotor activity in a novel environment than HiS rats (Carroll et al., 2008). On the other hand, similar to LCRs and HCRs, cohorts of HI and LI rats generally do not differ in their locomotor activity in a novel environment (Belin et al., 2008; Molander et al., 2011; Perry et al., 2005), although Dalley et al. (2007) found a negative correlation between impulsivity and novelty-induced locomotor activity. Likewise, with STs and GTs, no correlation was found between locomotor activity in a novel environment and sign-tracking, but a positive correlation was found between sign-tracking and novelty place preference (Beckmann et al., 2011; Robinson and Flagel, 2009). Finally, results are not consistent for a relationship between locomotor activity in a novel inescapable environment and novelty place preference, with HNP more active than LNP in one study (Beckmann et al., 2011) and no difference between groups in another (Belin et al., 2011).

3.2 Acute cocaine-induced locomotor activity and stereotyped behaviors

GTs, like HCRs, exhibit greater acute cocaine-induced locomotor activity than their ST counterparts (Flagel et al., 2008). RHA rats also exhibit greater activation than RLA rats after 5 or 10 mg/kg i.p. cocaine, as well as more pronounced stereotyped behaviors (i.e., rearing, sniffing and licking/gnawing; Giorgi et al., 2005; Lecca et al., 2004). Results for HRs and LRs, however, have been inconsistent with some studies finding HR's acute cocaine-induced activation greater than LR's activation but others finding no difference (Carey et al., 2003; Chefer et al., 2003; Hooks et al., 1991; Mantsch et al., 2001; Quertemont et al., 2004; Sell et al., 2005). The bHRs and bLRs, similar to the HiS and LoS rats, do not differ in acute cocaine-induced locomotor activity (Carroll et al., 2007; Garcia-Fuster et al., 2010). In summary, although several of these models show differential activation following acute cocaine, all of these models, unlike the LCR/HCR model, are based on behavioral differences that are apparent before drug exposure.

3.3 Repeated cocaine-induced locomotor activity: Behavioral sensitization

In contrast to our LCR/HCR model in which the lower initial cocaine-induced locomotor activity predicts the development of locomotor sensitization, both RHAs, which exhibit higher acute cocaine-induced locomotor activation, and HRs, which do not consistently differ from LR in their acute cocaine activation, more readily develop cocaine-induced locomotor sensitization (Chefer et al., 2003; Giorgi et al., 2005). Specifically, LR develop sensitization to a lesser extent than HRs; and RLAs do not develop sensitization at all. Interestingly, the selectively bred bHRs and bLRs differ from outbred HRs and LR in that horizontal cocaine-induced locomotion sensitizes similarly in both bHRs and bLRs; however, bHRs, but not bLRs, exhibit sensitization in their rearing responses to an acute cocaine injection after a 2-week withdrawal (García-Fuster et al., 2010). STs develop greater sensitization of head movements than GTs when exposed repeatedly to 15 or 30 mg/kg i.p. cocaine, but locomotor activity does not clearly sensitize in either group (Flagel et al., 2008). Lastly, HiS females develop only a weak cocaine-induced locomotor sensitization that does not persist when measured again 2 weeks later, and LoS females and HiS/LoS males develop no locomotor sensitization (Carroll et al., 2007). Again, the LCR/HCR model differs from these other models in that it is the lower acute cocaine locomotor responders that exhibit more reliable locomotor sensitization upon repeated exposure to cocaine.

4. Involvement of striatal DA systems

4.1 Introduction

Kalivas and Duffy (1990) demonstrated increased levels of extracellular DA in NAc after a challenge injection of cocaine in sensitized rats. Behavioral sensitization occurs not only in response to psychomotor stimulants like cocaine and amphetamine, but also to other addictive drugs like morphine, nicotine and alcohol, and to stress (Robinson and Berridge, 2001; Steketee and Kalivas, 2011). Sensitization is not manifested to the same extent or in the same behaviors in humans and non-human primates (Bradberry, 2007). Nevertheless, imaging studies in humans using the DA D2 receptor ligand [^{11}C]raclopride have demonstrated that: 1) the amphetamine-induced DA release initially observed in NAc spreads over time to the dorsal caudate and putamen and this progressive spread increases in response to repeated amphetamine (Boileau et al., 2006) and 2) the magnitude of cocaine-induced DA release in NAc positively correlates with lifetime stimulant use (Cox et al., 2009).

4.2 The LCR/HCR model – Role of striatal DA before and after acute cocaine

4.2.1 DA, the DAT and the vesicular monoamine transporter 2 (VMAT2)—

Cocaine's actions as a psychostimulant and reinforcer are most closely linked to its inhibition of plasma membrane DATs (Chen et al., 2006; Giros, et al., 1996; Ritz, et al., 1987; Thomsen et al., 2009). Thus, we investigated whether cocaine inhibition of striatal DAT activity differed between LCRs and HCRs and whether such differences contributed to the differential LCR/HCR cocaine-induced locomotor activation. To accomplish this, we used *in vivo* high-speed chronoamperometry to record clearance of locally-applied DA, a measure of DAT activity, in dSTR or NAc simultaneously with measurement of locomotor activity in individual chronically instrumented rats (Sabeti et al., 2002). No consistent LCR/HCR differences were observed in baseline DA clearance signal amplitudes or clearance efficiency in either brain region, or in basal locomotor activity. However, after an acute cocaine injection (10 mg/kg, i.p.), DA clearance was significantly inhibited in both brain regions of the HCRs over the same time period as their cocaine-induced hyperactivity but was not inhibited in the LCRs, whose cocaine-induced locomotor activity did not differ from saline-treated controls. Further, cocaine inhibition of DA clearance was more pronounced in NAc than in dSTR of the HCRs. Correlation analyses revealed that cocaine-induced changes

in striatal DA clearance parameters accounted for 20–40% of the rats' individual variation in acute cocaine-induced locomotor activation.

More recently, *in vivo* microdialysis studies provided remarkably parallel results for extracellular levels of DA in LCRs and HCRs (Nelson et al., 2009). Just as there were no differences in basal DA clearance or locomotor activity between LCRs and HCRs, there were also no LCR/HCR differences detected in basal extracellular DA in dSTR or NAc. Similarly, the greater acute cocaine-induced locomotor activity in HCRs was accompanied by greater increases in extracellular levels of DA in both striatal regions of HCRs than LCRs, with the difference being more pronounced in the NAc than dSTR. Thus, the *in vivo* DA clearance and extracellular DA results both support the idea that an acute low dose of cocaine significantly inhibits striatal DAT activity in HCRs, with the effect being greater in NAc than dSTR, thereby contributing to the more pronounced cocaine-induced increases in extracellular DA and locomotor activation in HCRs, as compared to LCRs (see model in Fig. 3).

To further characterize the role of DATs in the LCR/HCR phenotypes, we used *in vitro* binding of the cocaine congener [³H]WIN 35,428 and quantitative receptor autoradiographic analysis to measure DAT binding sites in dSTR, NAc shell, and NAc core (Nelson et al., 2009). Here we found the only consistent baseline difference that we have detected in LCRs vs. HCRs to date: their number of striatal DATs. While the LCR/HCR DAT binding sites did not differ in their affinity (K_d or K_i) for either [³H]WIN 35,428 or cocaine, LCRs had a significantly higher, by ~33%, number of DAT binding sites (B_{max}) in dSTR and NAc shell, with a similar trend ($p = 0.053$) in NAc core. This difference in B_{max} with a similar K_i for cocaine is consistent with LCRs being less sensitive than HCRs to the locomotor activation induced by a relatively low dose of cocaine because fewer DATs would be occupied by cocaine in LCRs, presumably still leaving sufficient DATs to clear extracellular DA in the striatum (Fig. 3). This reciprocal relationship between DAT number and DAT inhibitor efficacy has been elegantly demonstrated *in vitro* using a model cell system to vary the level of DAT expression (Chen and Reith, 2007). Our findings are also consistent with the idea that a higher dose of cocaine would not distinguish between LCRs and HCRs as readily as a lower dose. This is what we observed when we used 20 mg/kg, rather than 10 mg/kg, i.p. cocaine (Gulley et al., 2003).

Within DA neurons, DA is taken up by VMAT2 into vesicles from which it is released into the synapse. Using western blotting, we detected no differences in relative levels of VMAT2 in dSTR or NAc between LCRs and HCRs 30 min after an acute 10 mg/kg, i.p. cocaine injection (Richards, Ng and Zahniser, unpublished observations). When we examined [³H]DA uptake into striatal synaptosomes prepared from LCRs and HCRs after acute cocaine exposure, we were surprised to find that uptake velocity was significantly higher in HCRs than LCRs (by ~30%) at 25 and 30 min after cocaine (Briegleb et al, 2004; Mandt and Zahniser, 2010). The increased maximal uptake velocity (V_{max}) in HCRs became only a trend at 40 min, and there was no longer any LCR/HCR difference in V_{max} at 150 min post-injection (Mandt and Zahniser, 2010). Together, our results suggest that while LCRs have more basal DATs, which help to explain their lower initial cocaine-induced locomotor activation, HCRs appear to have a greater ability than LCRs to compensate for the acute cocaine inhibition and/or higher levels of extracellular DA by rapidly up-regulating DAT function and thereby limiting the time course of their cocaine-induced DA-mediated hyperactivity (Fig. 3).

It should be noted that while differences in cocaine inhibition of DATs significantly contributes to the LCR/HCR phenotypes, these differences do not completely account for the phenotypes. Differences in DA release could also contribute because cocaine has been

shown to preferentially enhance stimulation-evoked release of DA in NAc (Wu et al., 2001). Also, differences in striatal DA receptors/receptor signaling between LCRs and HCRs could be involved (see Section 4.2.2 below). Further, the time courses of the decay in cocaine-induced elevations in locomotor activation and extracellular DA are not identical, suggesting that desensitization of DA receptors and/or involvement of other neurotransmitter systems (NE, serotonin, glutamate, GABA, etc.) likely contribute to the LCR/HCR phenotypes.

4.2.2 DA D1 and D2 receptors—Because LCR/HCR differences may be partially explained by differences in DA receptor number or function, we compared levels of LCR/HCR DA receptor binding using the DA D1 receptor antagonist [³H]SCH23390 and the DA D2 receptor antagonist [³H]spiperone in membranes prepared 30 min after acute cocaine (10 mg/kg, i.p.) administration. No DA D1 or D2 receptor differences were detected between LCRs and HCRs in dSTR or NAc in either receptor number (B_{max}) or affinity (K_d; Table 3). To date, our results suggest that numbers of striatal D1 and D2 receptors are unlikely to play a major role in the LCR/HCR phenotypes, but we have not ruled out potential LCR/HCR differences in DA receptor signaling.

4.3 Other models – Role of DA before and after acute cocaine

DA and DA receptor differences have been reported in other rat models of individual differences that exhibit a differential response to cocaine. For example, while basal levels of extracellular DA in the NAc core and shell do not differ between RHAs and RLAs, acute cocaine (5 mg/kg, i.p.), morphine (0.5 mg/kg, s.c.), and amphetamine (0.15 mg/kg, i.p.) elicit a greater increase in extracellular DA in NAc shell than in NAc core of RHA, but not RLA, rats (Lecca et al., 2004). Further, the larger increase in extracellular DA in NAc shell of RHAs is associated with a more robust, drug-induced increase in locomotor response than in RLAs. Basal DA D1 and D3 receptor number is greater in NAc of RHA than RLA rats with no RHA/RLA difference in D2 receptor binding; however, RLA rats have greater D3 density in the Islands of Calleja (Giorgi et al., 1994; Guitart-Masip et al., 2006). These data suggest a higher DA tone in NAc shell in RHAs compared to RLAs, which could help to explain their locomotor response to novelty and acute cocaine: RHA>RLA (Giorgi et al., 2005; Steimer et al., 1997).

In contrast, HR/LR rats exhibit differences in NAc extracellular DA both basally and after acute cocaine (15 mg/kg; Hooks et al., 1991, 1992). Not only are basal levels of extracellular DA in NAc higher in HRs than in LR rats, but HRs also show greater acute cocaine-induced increases in extracellular DA in NAc than do LR rats. In addition, HRs have greater DA storage pools in NAc than LR rats, effectively allowing cocaine to release more DA from storage vesicles of HRs than LR rats (Verheij et al., 2008). This difference likely helps to account for the greater increase in cocaine-induced extracellular DA in NAc of HR than LR rats.

The selectively-bred bHR and bLR rats also display DA system differences (Flagel et al., 2010). Although total D2 receptor binding is similar in striatum, bHRs have a higher number of the functionally active form of the D2 receptor than bLRs. Further, bHRs have less D2 receptor mRNA, greater psychomotor response to the D2/3 agonist quinpirole, and more spontaneous DA transients in NAc core than bLRs.

Impulsivity has been shown to predict cocaine use and treatment retention in humans (Moeller, et al., 2001). Impaired inhibitory control resulting from chronic cocaine use can be manifested as increased impulsivity (Jentsch and Taylor, 1999). HI rats have significantly less DA D2/3 receptor availability in NAc than LI rats, independent of DA release (Dalley et al., 2007). D2/3 receptor deficiency in HI rats could explain their higher rates of cocaine self-administration during acquisition, similar to the high cocaine self-administration rates at high doses in mutant mice lacking D2-like receptors (Caine et al., 2002). However, as

mentioned in Section 4.2.2, although our lab has not detected DA D1 or D2 receptor differences in the dSTR or NAc of LCRs and HCRs, interestingly, when Stanis et al. (2008) measured impulsive choice in LCRs and HCRs using the delay-discounting task, HCRs behaved more impulsively than LCRs. Whether a similar relationship would be seen with tasks assessing impulsive action, such as the 5-CSRT task, or whether repeated cocaine exposure differentially changes impulsive behavior in LCRs and HCRs, remains to be determined. For example, cocaine-naïve HRs, which have higher basal levels of extracellular DA in the NAc (Hooks et al., 1992), were found to be more impulsive than LRs on a DRL task of impulsive action; but both phenotypes were equally sensitive to acute cocaine-induced increases in impulsivity on the DRL task (Stoffel and Cunningham, 2008).

4.4 The LCR/HCR model and other models – Role of DA after repeated cocaine

After repeated cocaine exposure, differences between LCRs and HCRs in striatal DAT number, cocaine inhibition of DA clearance and extracellular DA levels were no longer detected (Table 1). Specifically, in parallel with the development of locomotor sensitization induced by repeated cocaine exposure, cocaine inhibition of striatal DA clearance efficiency increased in the LCRs so that cocaine's ability to inhibit clearance no longer differed between LCRs and HCRs (Sabeti et al., 2003). Cocaine inhibition of clearance efficiency also remained similar in all rats after 7 days of withdrawal from repeated cocaine. Moreover, after repeated cocaine, no LCR/HCR differences in cocaine affinity for DAT, DAT number or cocaine-induced increases in extracellular DA levels in dSTR and NAc were detected (Nelson et al., 2009). Although these changes correspond with the development of locomotor sensitization in LCRs, we could not conduct the acute and repeated cocaine studies longitudinally in the same animals, making it impossible to conclude whether it was the LCRs and/or HCRs that had changed. Nevertheless, following repeated cocaine exposure a challenge dose of cocaine produced similar behavioral responses in LCRs and HCRs, which were paralleled by comparable effects of cocaine on striatal DATs and extracellular DA.

Most of the studies using other models have examined only basal or acute cocaine-induced differences in DA systems. However, one study has shown that after repeated cocaine RHAs exhibit a greater increase in extracellular DA in NAc core than after acute cocaine, whereas RLAs show no differences (Giorgi et al., 2007). These findings with the RHA/RLA model are in contrast with those in LCRs and HCRs, which after repeated cocaine no longer differ in extracellular DA levels in NAc (Nelson et al., 2009).

5. Involvement of glutamate systems

5.1 Introduction

It has been shown that ionotropic glutamate receptor signaling is required for development of locomotor sensitization in that antagonism of N-methyl D-aspartate receptors (NMDARs) or α -amino-3-hydroxy-5-methylisoxazole-4-propionate receptors (AMPA) prevents the development and/or the expression of locomotor sensitization (Wolf, 1998). Locomotor sensitization is also linked to changes in NMDAR and AMPAR subunits identified after repeated cocaine (Churchill, et. al., 1999). Furthermore, after repeated, but not acute, cocaine, extracellular glutamate increases in NAc only in rats that exhibit sensitized behaviors (Pierce, et. al., 1996; Yablonsky-Alter, et. al., 2009). Because LCRs more readily than HCRs develop locomotor sensitization (Allen et al., 2007; Mandt et al., 2008, 2009; Nelson et al., 2009, 2010; Sabeti et al., 2003; Yamamoto and Zahner, 2012), we were interested to determine if ionotropic glutamate receptors and/or extracellular glutamate levels could help to explain LCR/HCR differences. To our knowledge, the other rat models

of individual differences discussed above have not reported any studies investigating glutamate.

5.2 The LCR/HCR model – Role of glutamate after acute and repeated cocaine

5.2.1 Extracellular glutamate in NAc—The glutamatergic projection from the dorsal prefrontal cortex (dPFC) to the NAc core is important for behavioral sensitization, as well as for cocaine- and stress-induced reinstatement of cocaine self-administration. Microdialysis studies have shown that ibotenic acid lesions of the dPFC block experimenter delivered cocaine-induced expression of behavioral sensitization and increase extracellular glutamate levels in the NAc core (Pierce et al., 1996). Self-administration studies further show that inactivation of the dPFC before cocaine blocks both the increased extracellular glutamate in the NAc core and reinstated lever pressing in rats (McFarland et al., 2003, 2004). Thus, we investigated whether changes in extracellular glutamate in NAc play a role in our observation that LCRs develop locomotor sensitization more readily than HCRs in response to repeated cocaine (Allen et al., 2007; Mandt et al., 2008, 2009; Nelson et al., 2009, 2010; Sabeti et al., 2003; Yamamoto and Zahniser, 2012).

We used *in vivo* microdialysis to test for differences between LCRs and HCRs in extracellular glutamate levels in NAc basally, after acute cocaine (10 mg/kg, i.p.), on day 7 of once-daily repeated 10 mg/kg cocaine treatments or upon 10 mg/kg cocaine challenge after 1 week withdrawal from repeated cocaine exposure. Saline controls were also included in each experiment. Dialysis probes were implanted unilaterally (acute) or bilaterally (repeated) into the NAc ($\pm 6^\circ$ angle from vertical, 1.6 mm anterior, ± 2.4 mm lateral to bregma, 6.0 mm below dura) using coordinates from Paxinos and Watson (2007). Dialysate samples (20 μ l) were collected every 10 min for 2 hr pre-injection of cocaine or saline (baseline) and 2 hr post-injection. Glutamate levels were measured using high performance liquid chromatography with electrochemical detection following derivitization with o-phthalaldehyde (Lalumière and Kalivas, 2008). The limit of detection was 0.01 μ M glutamate. Two-way (time $\times$ group) RMANOVAs were used to compare extracellular glutamate concentrations followed by ANOVAs and post-hoc comparisons. Only animals with histologically confirmed probe placements in NAc were included in the data analysis. Baseline extracellular glutamate levels did not differ between LCRs, HCRs and saline controls in any of the three experiments (Table 4). To our surprise, we also detected no differences between glutamate levels in LCRs, HCRs and saline controls post-injection even though the expected differences in locomotor activity were observed (Yamamoto and Zahniser, unpublished observations). Our results suggest that extracellular glutamate in NAc does not help to explain the maintenance of locomotor sensitization to 10 mg/kg cocaine in the LCRs. However, we have not yet measured extracellular glutamate in NAc during development of sensitization or in dSTR of LCRs and HCRs (see Section 5.2.2 below).

5.2.2 AMPAR and NMDAR subunits—We used semi-quantitative western blotting to investigate whether AMPARs and/or NMDARs help to explain the differential sensitivity of LCRs and HCRs to the locomotor-stimulant effects of low dose cocaine. To do this, we examined total protein levels of GluA1 and GluA2 subunits (AMPARs) and GluN2A and GluN2B subunits (NMDARs) in dSTR, NAc and ventral tegmental area (VTA), as well as phosphorylation of GluA1 at Ser-845 and Ser-831, and GluN2B at Tyr-1472 and Ser-1303, in dSTR and NAc 40 min after acute cocaine exposure (Yamamoto and Zahniser, 2012). Further, we examined cell surface GluA1, GluA2, and GluN2B subunits in dSTR and NAc 40 min after acute cocaine. We found no LCR/HCR differences in total or cell surface receptors. However, we observed a significant LCR/HCR difference in Tyr-1472 phosphorylation of GluN2B in dSTR. Compared to HCRs, the levels of pGluN2B^{Tyr-1472} in LCRs were 40% higher 40 min after acute cocaine treatment. Although HCRs' locomotor

activation reaches its peak at 20–30 min and has begun decreasing by 40 min, it is still significantly increased compared to LCRs at this time. Further, pGluN2B^{Tyr-1472} levels in dSTR had a significant inverse relationship with cocaine-induced locomotor activity in all of the rats, regardless of LCR/HCR classification. There was a similar trend ($p = 0.08$) for a negative correlation between cocaine-induced locomotor activity and the phosphorylation state of GluN2B^{Tyr-1472} in NAc. Next, we examined total and cell surface glutamate receptor subunits and phosphorylation sites as just described 40 min after day 7 of repeated 10 mg/kg, i.p. cocaine, but found no LCR/HCR differences (Yamamoto and Zahniser, 2012).

Enhanced phosphorylation of pGluN2B^{Tyr-1472} increases surface expression of NR2B-containing NMDARs (Cary et al., 2012; Zhang et al., 2008). We cannot say definitively if the LCR/HCR differences in pGluN2B^{Tyr-1472} in dSTR occur in response to acute cocaine exposure or are innate because currently we are unable to classify rats as LCRs or HCRs without first injecting them with a single dose of cocaine. Nonetheless, the greater dSTR pGluN2B^{Tyr-1472} after acute cocaine in LCRs, but not HCRs, may enhance the sensitivity of post-synaptic neurons in LCRs to glutamate and, thus, contribute to their plasticity and preferential development of locomotor sensitization, as compared to HCRs.

6. Other behaviors – The LCR/HCR model and other models

6.1 Drug discrimination (cocaine)

Klein and Gulley (2009) have used the LCR/HCR model to test the interoceptive effects of cocaine. In this study, only rats with an acute cocaine-induced locomotor response in the upper and lower thirds were included. Male Long-Evans rats classified as LCRs or HCRs were trained to discriminate cocaine (10 mg/kg, i.p.) from vehicle using an operant chamber and food reinforced responding. Subsequently, the rats were tested with a range of cocaine doses (1.25 – 15 mg/kg, i.p.), and LCRs showed partial-to-full generalization to lower doses of cocaine (1.85 and 2.5 mg/kg cocaine). In contrast, HCRs showed no such generalization. These results suggest an inverse relationship between the initial locomotor stimulant effects and the discriminative stimulus properties of cocaine. Thus, although LCRs appear less sensitive to the locomotor stimulant effects of cocaine, interestingly they appear to be more sensitive to the drug's interoceptive properties, particularly at low doses. This finding underscores that the "low cocaine response" of LCRs, versus HCRs, refers to cocaine-induced locomotor activity.

6.2 Reward: Psychostimulant CPP

6.2.1 The LCR/HCR model—CPP is used to determine the rewarding or aversive effects of a drug by measuring the amount of time spent in a previously drug-paired chamber. Recently, it has been reported that humans develop a preference for an amphetamine-paired room over an unpaired room (Childs and de Wit, 2009, 2011). Further, the subjects reported increased stimulation and drug craving after amphetamine on the second administration, helping to validate the use of CPP as a model to study addiction-like behaviors in animals. To address whether LCR/HCR classification predicted development of cocaine-induced CPP, we assessed locomotor activity, locomotor sensitization and CPP concurrently (Allen et al., 2007). Rats were readily classified as LCRs and HCRs using 1 mg/kg i.v. cocaine. Further, LCRs, but not HCRs, developed both CPP and locomotor sensitization. In this study, which consisted of two daily training sessions (cocaine and saline once each day) for 4 days, 10 mg/kg, i.p. produced locomotor sensitization in LCRs, but not HCRs; however, neither group developed CPP.

Since the lack of CPP in response to 10 mg/kg i.p. cocaine in our first CPP experiment could have been due to the compressed training schedule (Allen et al., 2007), more recently we tested a group of rats trained once daily for 8 days with 10 mg/kg, i.p. cocaine or saline on alternate days. Under these conditions, LCRs, but not HCRs, readily developed both CPP (Fig. 4) and locomotor sensitization (Barcomb, Yamamoto, Allen, and Zahniser, data not shown). Thus, we found that LCR/HCR classification is predictive of later development of i.v. or i.p. cocaine CPP, with LCRs being the more sensitive phenotype to the rewarding properties of cocaine.

6.2.2 Other models—CPP experiments have produced mixed results in the HR/LR model. In studies using male Sprague-Dawley rats, HRs and LRs develop CPP equally well to both cocaine and amphetamine (Erb and Parker, 1994; Gong et al., 1996; Kosten and Miserendino, 1998). However, in another study using Long-Evans rats, a negative correlation between novelty activity and cocaine or amphetamine CPP was revealed at low doses (Mathews et al., 2010). Differences in rat strains, drug doses and/or experimental conditions may account for this discrepancy. A recent study in male Sprague-Dawley rats found that, although HRs and LRs do not differ in development of cocaine CPP, HRs maintained a stronger conditioned preference than LRs when retested 30 days post-conditioning (Capriles et al., 2012). In other studies, the behavioral traits of high novelty seeking and high impulsivity in Sprague-Dawley rats have been found to predict amphetamine CPP (Klebaun and Bardo, 1999; Yates et al., 2012).

6.3 Reinforcement – cocaine self-administration

It is important to assess the direct reinforcing and motivational properties of cocaine in any animal model of addiction. This can be accomplished with self-administration, in which animals press a lever to receive an i.v. infusion of drug. Self-administration has predictive validity for the abuse liability of a number of drugs and is a commonly accepted method for studying individual differences in animal models of addiction (O'Connor et al., 2011). While the simple act of drug self-administration by an animal does not equal addiction, this procedure enables researchers to investigate components of the addiction process including: acquisition and maintenance, “motivation” (i.e., break point; BP), extinction and reinstatement, as well as other “addiction-like” behaviors. 24

6.3.1 The LCR/HCR model: Acquisition and motivation—We chose to start our investigations of self-administration behavior in LCRs and HCRs by conducting an acquisition experiment, allowing us to assess the reinforcing effectiveness of cocaine from the earliest point of the LCRs' and HCRs' exposure to the drug. This initial experiment consisted of testing for LCR/HCR differences in latency to acquire low-dose cocaine self-administration (0.25 mg/kg/infusion delivered over 12-sec) under a fixed ratio 1(FR1) schedule of reinforcement (Mandt et al., 2008). Latency to acquisition was determined in LCRs and HCRs following both single cocaine pre-exposure (i.e., for classification; 1 day of 10 mg/kg, i.p.) and repeated cocaine pre-exposure (5 days of once-daily 10 mg/kg, i.p.) conditions. Surprisingly, this initial study did not reveal LCR/HCR differences in the acquisition of cocaine self-administration under either acute or repeated pre-exposure conditions (Mandt et al., 2008). Further, whereas LCRs again developed cocaine-induced locomotor sensitization and HCRs did not, all rats receiving repeated cocaine pre-exposure more readily acquired cocaine self-administration than rats receiving a single pre-exposure, regardless of the development of cocaine-induced locomotor sensitization.

We have since conducted a more thorough assessment of acquisition in LCRs and HCRs using a wider range of cocaine doses (0.14, 0.29, 0.38, 0.77, and 1.15 mg/kg i.v. infusion delivered over 6-sec; Mandt et al., 2012b). Despite extensive testing, we have not found

LCR/HCR differences in the acquisition of cocaine self-administration. Interestingly, a recent study by Schramm-Sapota et al. (2011) that analyzed a number of individual differences, including locomotor response to cocaine, found that a high initial locomotor response to cocaine (10 mg/kg, i.p.) positively correlated with active lever pressing (0.8 mg/kg/i.v. infusion). Notably, there were significant experimental differences between that study and ours making direct comparison difficult (e.g., differences in cocaine dose, reinforcement schedules, rats pre-trained to respond for food, etc.). Regardless, acquisition is an important first assessment of self-administration behavior and clear LCR/HCR differences in this measure have not emerged. However, because factors other than drug effects also impact acquisition (e.g., learning mechanisms) and FR1 schedules of reinforcement can make interpretation of a drug's reinforcing effectiveness difficult (Richardson and Roberts, 1996), it is necessary to examine additional measures of self-administration behavior.

Following acquisition testing in our initial self-administration study, LCRs and HCRs were tested for their "motivation" to respond for a range of cocaine doses (0.25, 0.5, and 1 mg/kg/infusion over 12-sec) under a progressive ratio (PR) schedule of reinforcement (Mandt et al., 2008). In contrast with their similar acquisition rates, here LCRs and HCRs were found to differ in how hard they would work to self-administer cocaine. Under both the single and repeated pre-exposure conditions, LCRs exhibited significantly greater BPs (i.e., "motivation") than HCRs at each of the doses tested. Similar to acquisition, all rats given repeated pre-exposure also exhibited greater BPs than rats receiving a single pre-exposure, regardless of the development of cocaine-induced locomotor sensitization. It is important to restate, however, that even though HCRs in the repeated pre-exposure condition exhibited increased BPs, they still exhibited lower BPs than LCRs in the repeated pre-exposure condition. Thus, under low-dose conditions, LCRs have been found to exhibit increased "motivation" to self-administer cocaine compared to HCRs. Highlighting the importance of BP, this dependent measure is one of the criteria included in an "animal model" of addiction diagnostic criteria (Deroche-Gamonet et al., 2004).

A more recent study assessing the development of sensitization to the motivational effects of cocaine during self-administration on a PR schedule did not find differences between LCRs/HCRs in BP over the course of 10 post-acquisition PR sessions (Mandt et al., 2012a). Noteworthy, rats in the initial self-administration study were trained to self-administer a very low dose of cocaine (0.25 mg/kg/i.v. infusion delivered over 12-sec) before exposure to higher doses of cocaine (0.25, 0.5, or 1.0 mg/kg/i.v. infusion) for short periods of time (i.e., two self-administration sessions at each dose). In contrast, rats in the later study acquired self-administration of a more moderate dose of cocaine (0.6 mg/kg/i.v. infusion delivered over 6-sec) before self-administering this dose or a higher dose (0.6 or 1.2 mg/kg/i.v. infusion delivered over 6-sec) for 10 additional sessions. The differences in drug sensitivity between LCRs and HCRs at low doses may be overcome at moderate to high doses, similar to other models of individual differences (e.g., Mantsch et al., 2001; see below). Thus, the low vs. moderate doses used during the self-administration period prior to PR testing may contribute to the discrepancies in our results. Overall, our findings for acquisition and motivation to self-administer cocaine indicate that 1) LCRs and HCRs do not appear to differ in the acquisition of cocaine self-administration and 2) low doses and slow infusion rates during acquisition reveal LCR/HCR differences in motivation to self-administer cocaine. We are currently investigating additional measures of "addiction-like" self-administration behaviors in LCRs and HCRs.

6.3.2 Other models: Acquisition and motivation—It has been shown that HRs and LR differ in acquisition of low dose cocaine self-administration (Mantsch et al., 2001; Marinelli and White, 2000; Piazza et al., 2000). Under short access conditions (1hr/day),

HRs, but not LR rats, acquire cocaine self-administration at 0.1 and 0.175 mg/kg/i.v. infusion (Marinelli and White, 2000; Piazza et al., 2000). In contrast, under extended access conditions (10 hr/day and 0.25, 0.5, 1.0, or 2.0 mg/kg/i.v. infusion) both HRs and LR rats acquire, but HRs acquire more readily and consume more cocaine than LR rats only at the lowest dose tested (0.25 mg/kg; Mantsch et al., 2001). Conversely, at 1.0 mg/kg/i.v. infusion, HR rats self-administer less than LR rats, while there are no HR/LR differences in acquisition at 0.5 and 2.0 mg/kg/i.v. infusion, again suggesting that differential sensitivity to a drug can be overcome by longer exposure times and/or higher doses.

Similarly, RHA rats respond at a higher rate than RLAs during cocaine acquisition training (Fattore et al., 2008), and HiS rats more readily acquire cocaine self-administration than LoS rats (Carroll et al., 2008). Generally, HI and LI rats acquire cocaine self-administration at similar rates (Anker et al., 2009; Belin et al., 2008; Broos et al., 2012; Dalley et al., 2007), but one study showed a greater percentage of HI rats acquire cocaine self-administration and at a faster rate than LI rats (Perry et al., 2005). HI rats lever press more and exhibit a vertical shift in the dose-response curve for cocaine, compared to LI rats (Dalley et al., 2007). Furthermore, HI rats escalate cocaine-reinforced responding under extended access conditions whereas LI rats do not (Anker et al., 2009).

In contrast to the models discussed above but similar to the LCR/HCR model, HNP and LNP acquire cocaine self-administration (0.8 mg/kg/infusion) at comparable rates (Belin et al., 2011). STs and GTs do not differ in acquisition of cocaine self-administration at 0.5 mg/kg/infusion (Saunders and Robinson, 2010); however, Beckmann et al. (2011) found that at a lower dose (0.3 mg/kg/infusion) there was a positive correlation between cocaine acquisition and sign-tracking but no correlation at 1.0 mg/kg/infusion. Further, STs exhibited higher BPs than GTs at 0.2 mg/kg/infusion (Saunders and Robinson, 2011). On the other hand, no differences have been revealed between BPs for HI and LI rats (Anker et al., 2009; Belin et al., 2008; Broos et al., 2012).

HRs and LR rats do not differ in a 3-criteria measure of compulsive drug taking and seeking: BP on a PR schedule of reinforcement, persistent responding when signal says 'no drug available', and resistance to punishment (Belin et al., 2011). In contrast, HNP and LNP rats differ in compulsive drug taking and seeking, with HNP>LNP (Belin et al., 2011). Based on these results, it was proposed that HRs, with their higher acquisition and responding rates, are "drug use prone" but that HNPs, with their compulsive drug seeking, are "addiction prone." Interestingly, when HRs and LR rats were selectively bred for differential locomotor activity in a novel environment, some aspects of the phenotype changed. Like the outbred HRs, bHRs acquire cocaine self-administration faster and self-administer cocaine more than bLRs; however, unlike HRs, bHRs also exhibit a higher BP than bLRs over a range of drug doses (Cummings et al., 2011; Davis et al., 2008). Flagel et al., (2010) reported that bHRs also learn to approach a food or cocaine cue, making them STs and bLRs do not, making them GTs.

6.3.3 Other models: Extinction and reinstatement—One study showed STs exhibit greater cue-induced reinstatement and are resistant to extinction relative to GTs (Saunders and Robinson, 2010). However, while a more recent study found greater cocaine-induced reinstatement, the extinction rates between STs and GTs were similar (Saunders and Robinson, 2011). These results suggest that STs may be an "addiction prone" phenotype like the HNPs and in contrast to the "drug use prone" outbred HRs, labeled as such because of their overall lack of compulsive cocaine self-administration (Belin et al., 2011). Like the STs, HI rats trained to self-administer cocaine are also more resistant to extinction and exhibit a greater propensity to context-induced relapse than LI rats (Broos et al., 2012). In addition, male HI rats resemble 3-criteria, "addiction prone," rats, with higher BPs,

resistance to punishment, and persistent drug seeking, unlike the “drug use prone” HRs (Belin et al., 2008, 2011). There is evidence for marked differences in the brain circuitry critical for early drug use and later addiction and relapse states (Koob and Volkow, 2010) and it has been suggested that impulsivity could be used as a predictor of addiction. However, it is important to note that impulsivity tests are specific for either impulsive choice or impulsive action, which measure different aspects of drug taking and seeking (Broos et al., 2012). Further, there is evidence that these tests involve different neural substrates as well (Pattij and Vanderschuren, 2008; Winstanley et al., 2006).

In future studies we will determine if LCRs and HCRs differ in extinction from cocaine self-administration and reinstatement. In light of the higher impulsivity of HCRs, it would also be interesting to pursue additional behavioral studies, such as the goal-tracking/sign-tracking test or an impulsive action test such as the 5-CSRT task, in order to further characterize the LCRs or HCRs as “drug-use prone” and/or “addiction-prone”. Further, these tasks are predictive of cue-induced reinstatement. If differences do exist between LCRs and HCRs in these tests, the results may help to predict differential LCR/HCR responsiveness to cue-induced reinstatement after being extinguished from cocaine self-administration.

7. Conclusions

Initial response to cocaine varies among individuals; it can be predictive of future drug dependence and influences the subjective value of cocaine after chronic use in humans (Davidson et al., 1993; Goldstein et al., 2010; Lambert et al., 2006). Although human imaging studies have provided valuable information about differences in brain function of addicts as compared to controls, animal models allow us to investigate behavioral responses to abused drugs and underlying biochemical mechanisms that currently cannot be addressed in human studies. Our group has developed the LCR/HCR model as a useful tool to study individual differences in cocaine addiction-like behaviors. A unique aspect of this model is that it is based on individual rats’ initial response to drug, specifically their initial activation to a low dose of cocaine. This model is also valuable because it helps to explain the variability within groups of outbred rats in their responsiveness to low dose cocaine and development of cocaine locomotor sensitization, both of which many groups have observed over the years. We have identified behavioral and biochemical differences with the LCR/HCR model that help to explain the HCRs’ greater initial response to cocaine and the LCRs’ more ready development of addiction-like behaviors. Table 1 summarizes our findings to date with the LCR/HCR model.

One unique aspect that distinguishes the LCR/HCR model from the other models of individual differences summarized in Table 2 is that it is based on locomotor response to cocaine, not on baseline behavioral parameters. Comparing the LCR/HCR model to the HR/LR model, which is one of the most well-studied models, we note that, in addition to the difference in novelty response ($HR > LR$; $LCR = HCR$), and acute cocaine-induced locomotor activity ($LCR < HCR$; $HR \sim LR$), HRs develop cocaine sensitization to a larger degree than LR, while LCRs, with consistently lower acute cocaine activation, develop sensitization. The HR/LR model also differs from the LCR/HCR model both in acquisition of cocaine self-administration and in motivation to self-administer cocaine. Both LCRs and HCRs acquire cocaine self-administration similarly at all doses tested (Mandt et al., 2008; Mandt et al., 2012b). In contrast, cocaine acquisition varies between HRs and LR depending on dose and/or exposure time (Belin et al., 2008; Kabbaj et al., 2001; Mantsch et al., 2001; Marinelli and White, 2000; Piazza et al., 2000). Further, whereas LCRs exhibit higher BPs for cocaine than HCRs under low dose conditions (Mandt et al., 2008), HRs and LR do not differ in BP on a PR schedule of reinforcement (Belin et al., 2008, 2011).

Corticosterone levels may, in part, help explain the differences between the HR/LR and LCR/HCR models. HRs have higher and longer elevated plasma corticosterone than LR in response to a novel environment (Kabbaj et al., 2000, Piazza et al., 1991, Piazza et al., 1998). Further, in the NAc, HRs have similar (Chefer et al., 2003) or higher (Hooks et al., 1992) basal levels of extracellular DA than LR and show greater acute cocaine-induced increases than LR. In Fisher 344 rats, corticosterone treatment has been shown to increase tyrosine hydroxylase, the rate limiting enzyme in DA synthesis, and to cause locomotor sensitization to cocaine (Ortiz et al., 1995). Higher plasma corticosterone levels may affect basal levels of extracellular DA in NAc of HRs, which in turn could influence their locomotor response to novelty: HRs > LR. In contrast, corticosterone does not explain LCR/HCR behavior as there are no group differences in plasma corticosterone levels basally, after exposure to a novel environment, or after acute and repeated cocaine treatments (Nelson et al., 2010). Further, basal extracellular DA levels in LCR/HCRs do not differ; and after acute cocaine, extracellular DA increases more in HCRs than LCRs in both NAc and dSTR, indicating no relationship between levels of DA and corticosterone in LCRs and HCRs.

The model that has the most behavioral similarities to the LCR/HCR model is the ST/GT model (Table 2). Neither group in either model differs in locomotor activity in a novel environment; however, a positive correlation was found between sign-tracking and novelty place preference (Beckmann et al., 2011; Robinson and Flagel, 2009). In contrast, we have found no difference in novelty place preference between LCRs and HCRs, as measured in a CPP paradigm (Allen et al., 2007). STs, like LCRs show lower acute-cocaine increases in locomotor activity and greater sensitization to repeated cocaine (Flagel et al., 2008). However, unlike LCRs, STs develop sensitization in head movements; but neither STs nor GTs develop horizontal locomotor sensitization. At 0.3 mg/kg/infusion, there is a positive correlation between cocaine acquisition and sign-tracking, but at higher doses (0.5 and 1.0 mg/kg/infusion) STs and GTs, like LCRs and HCRs, do not differ in acquisition of cocaine self-administration (Beckmann et al., 2011, Saunders and Robinson, 2010). Similar to LCRs, STs exhibit higher cocaine BPs than GTs (Saunders and Robinson, 2011). STs also show greater cue and cocaine reinstatement, but either equal or greater resistance to extinction compared to GTs (Saunders and Robinson, 2010, 2011). To date, there are no reported ST/GT studies comparing basal and cocaine-induced extracellular DA or DAT levels and function; thus, it remains to be seen if DA systems explain some of the differences between the LCR/HCR and ST/GT models.

Based on the results before and after acute cocaine administration, we conclude that the number of striatal DATs and acute cocaine-induced changes in striatal extracellular DA, in particular in NAc, play an important role in the initial classification of LCRs and HCRs. Specifically, we found that basally LCRs have a greater number of striatal DATs than HCRs, leaving the LCRs with sufficient functional DATs after acute low dose cocaine inhibition to take up excess extracellular DA (Fig. 3). HCRs, with fewer DATs, experience significant acute cocaine-induced DAT inhibition and thus higher levels of DA would remain and stimulate DA receptor-mediated signaling for longer periods of time. These findings help to explain the greater acute cocaine-induced increase in locomotor activity in HCRs, as compared to LCRs. As mentioned previously, cocaine-induced changes in DA release (Wu et al. 2001) and/or DA receptor signaling differences revealed in the presence of cocaine could also contribute to the LCR/HCR phenotypes. These possibilities remain to be explored. Interestingly, HCRs rapidly up-regulate their striatal DAT function following cocaine exposure, and this rapid regulation may help to protect the HCRs against repeated cocaine-induced neuroplasticity and behavioral changes such as locomotor sensitization. In contrast, the increased NMDAR GluN2B^{Y-1472} phosphorylation in LCRs' dSTR observed after acute cocaine could help to prime striatal neuroplasticity and thereby contribute to the

preferential development of repeated cocaine-induced locomotor sensitization and the development of CPP in LCRs, as compared to HCRs (Maldonado et al., 2007; Wolf 1998). In addition to the importance of DATs, DA and glutamate, cocaine inhibition of NET and SERT, and the resulting increases in NE and serotonin, could also contribute to the differential behavioral effects of cocaine in LCRs and HCRs. Thus, it will be important in future studies to ascertain if there are LCR/HCR differences in the number and/or function of these transporters.

From human studies it is not yet clear how DAT number, as determined from brain imaging studies, and the response of individuals to psychostimulants are related. These studies have focused on DAT polymorphisms and other DAT variants, which can affect DA availability in the synapse. The polymorphism most studied on the *DAT1* gene is a 40-base pair (bp) variable number tandem repeat (VNTR) within the 15th exon, located in the 3' untranslated region (3'-UTR; Vandenberg et al., 1992). This VNTR may be evolutionarily recent, as it has been observed in humans, chimpanzees and cynomolgous macaques, but not in rats or mice (Dreher et al., 2009). Studies of the two resulting major 9- and 10-repeat alleles of the 3'-UTR have yielded variable results as to DAT expression (Cheon et al., 2005; Heinz et al., 2000; Joos et al., 2007; van de Giessen et al., 2009; van Dyck et al., 2005). An additional, and less well-studied, VNTR has been discovered in the 8th intron of *DAT*; and the 3-repeat allele of this VNTR was associated with increased levels of *DAT1* (Brookes et al., 2007). A strong association between cocaine dependence and this 3-repeat allele was found in humans (Guindalini et al., 2006). A recent study testing the relationship between DAT brain availability (Bmax/Kd) and DAT genotypes (3'-UTR, and intron 8- VNTRs) in healthy subjects indicated that both polymorphisms modulate DAT density as single genetic markers and in combination, as haplotypes; however, ethnicity and age modulate these associations (Shumay et al., 2011). Further studies are needed to determine the importance of these polymorphisms for initial responsiveness to and abuse of cocaine. In future animal studies, selective breeding could be useful to determine if the *DAT1* gene is associated with LCR/HCR differences in striatal DAT expression.

We would also like to emphasize that although LCRs are less sensitive to the acute locomotor stimulant effects of cocaine, they are more sensitive to the interoceptive properties of cocaine (Klein and Gulley, 2009). Just as initial response in humans can influence the later subjective value of cocaine, LCRs' greater ability to discriminate low doses may increase cocaine's salience and reward valence. This greater discrimination in LCRs may also influence their motivation to self-administer the drug when trained with a very low dose, as well as possibly having an impact on relapse to drug seeking after withdrawal. Future studies will be needed to determine if there are LCR/HCR differences in drug-, cue-, and/or stress-induced relapse to cocaine seeking, and if so, under what conditions these differences are apparent.

As impulsivity has been linked to substance abuse, the finding of Stanis et al. (2008) that HCRs are more impulsive on the delay discounting task raises the question of how they will respond in other impulsive measures, such as impulsive action, and whether there are LCR/HCR differences in impulsivity after repeated cocaine. Differentiating the specific vulnerabilities of an individual to a drug of abuse like cocaine should provide insights into preventing and/or treating this devastating problem.

Overall, our studies have highlighted important differences between LCRs and HCRs in behavioral tests that model particular aspects of addiction (Table 1). First, LCRs more readily and to a greater degree than HCRs develop cocaine-induced locomotor sensitization, which has been associated with increased incentive salience, drug craving, and relapse to drug seeking (Robinson and Berridge, 2001). Second, LCRs, but not HCRs, develop cocaine

CPP. To the best of our knowledge, cocaine-CPP has not been consistently reported in the other animal models of individual differences described here, making our findings unique. Human subjects develop a preference for an amphetamine-paired room and report increased stimulation and drug craving in the drug paired room (Childs and de Wit, 2009, 2011). This report underscores the importance of this difference in LCRs/HCRs. Third, LCRs display greater motivation, under some conditions, to self-administer cocaine than HCRs in an animal model of drug reinforcement. Specifically, it appears that low doses given over a longer time (0.25 mg/kg/i.v. infusion over 12-sec) during cocaine self-administration acquisition training predict LCR/HCR differences in BPs for a range of doses (0.25, 0.5, 1.0 mg/kg/i.v. infusion delivered over 12-sec), which is surmountable by acquisition training using a higher dose given over a shorter time (0.6 mg/kg/i.v. infusion over 6-sec). It will be important to test a range of doses to determine if there are LCR/HCR differences in extinction and reinstatement (relapse) to cocaine seeking. Based on these initial studies, we conclude that LCRs, as compared with HCRs, may be more “addiction prone” and that the LCR/HCR model, based on individual differences in the hyperactivity response to acute low dose cocaine, is a valuable addition to the tools for drug addiction research.

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Highlights

- Outbred Sprague-Dawley rats differ in acute cocaine-induced locomotor activity.
- Rats are classified as low or high cocaine locomotor responders (LCRs or HCRs).
- LCRs have higher basal numbers of striatal dopamine transporters (DATs) than HCRs.
- LCRs display greater cocaine-induced locomotor sensitization and reward than HCRs.
- LCRs are more motivated to self-administer cocaine than HCRs under low-dose conditions.

Figure 1.

Classification of outbred male Sprague-Dawley rats as LCRs or HCRs. **(a)** Representative results show the range of magnitudes and time course of locomotor activity in the open field for 16 individual rats 90 min before and 30 min after an injection of 10 mg/kg, i.p. cocaine (arrow). **(b)** The range of novelty (first 30 min), baseline (30 min before injection), and 30 min post-injection activity is shown for saline control rats ($n=6$; horizontal line=median) and cocaine-treated rats ($n=16$; 10 mg/kg, i.p.). Classification of the cocaine-treated rats as LCRs ($n=8$; mean values $\pm$ SEM) or HCRs ($n=8$) was based on the group median split. **(c)** Time course of locomotor activity is shown as described in (a), but with rats separated into LCR ($n=8$), HCR ($n=8$), and saline control ($n=6$) groups.

Figure 2.

No LCR/HCR differences in cortical cocaine levels or correlation with distance traveled after acute or repeated cocaine. **(a,c)** LCR/HCR cortical cocaine levels were similar 40 min after acute cocaine **(a)**; LCR=1.07±0.13ng/mg, HCR=1.09±0.16, mean values±SEM) and 40 min after cocaine injection on day 7 **(c)**; LCR=1.08±0.14 ng/mg, HCR=0.99±0.11). The percent recovery based on the cocaine propyl ester-HCl internal standard was 0.78±0.01 for acute cocaine and 0.85±0.02 for repeated cocaine. **(b,d)** Locomotor activity (distance traveled in 30 min post-injection) and cortical cocaine levels 40 min post-injection were not correlated in the individual rats after acute cocaine **(b)** or repeated cocaine **(d)**.

Figure 3.

Working model for the effects of acute cocaine on DATs in striatum of LCRs (left) and HCRs (right). **a)** Basally, LCRs have a greater number of DATs than HCRs but exhibit similar levels of extracellular DA and locomotor activity. **b)** 10–20 min after acute cocaine (10 mg/kg, i.p.), the same percentage of DATs is inhibited by cocaine in LCRs and HCRs because their DATs have similar affinity for cocaine. This leaves more DATs unoccupied by cocaine in LCRs, as compared to HCRs. In HCRs this difference results in slower clearance of extracellular DA, greater cocaine-induced increases in extracellular DA, more DA receptor (DR) stimulation and signaling, and greater locomotor activity than in LCRs. **c)** At ~35 min after acute cocaine, LCR/HCR DAT differences have been eliminated as a result of rapid DAT up-regulation in HCRs (shown here as an increased number of DATs, but also could reflect a functional up-regulation; Mandt and Zahniser, 2010). Brain cocaine levels have peaked and are declining. This results in declining extracellular DA, DR stimulation and signaling, and locomotor activity in HCRs. Adapted from the doctoral dissertations of Drs. Anna Nelson and Bruce Mandt.

Figure 4.

CPP in LCRs, but not HCRs, after i.p. cocaine conditioning. Pre- and postconditioning preferences (% time spent in drug-paired compartment) were calculated after 8 once-daily conditioning trials with 10 mg/kg i.p. cocaine or saline alternated every other day or with 8 once-daily conditioning trials with saline (controls). When control rats (n=6) were compared to all cocaine-injected rats (n=16), Repeated Measures Analysis of Variance (RMANOVA) revealed an interaction between session and group [$F(1,20)=12.94$, $p=0.0018$]. Post-hoc analyses revealed that only cocaine-conditioned rats increased time spent in the cocaine-paired compartment (paired-samples t-test, $t(15)=3.831$, $p=0.016$). When control rats were compared to cocaine-conditioned rats classified as LCRs (n=8) or HCRs (n=8), again the RMANOVA revealed an interaction between session and group [$F(2,19)=7.19$, $p=0.004$]. One-way ANOVAs revealed between-group differences for post-conditioning preferences only [$F(2,19)=5.674$, $p=0.0117$]. Post-hoc t-tests revealed that only LCRs showed a significant change in preference [pre- vs. post, $t(7)=3.275$, $p=0.0136$]. Between group post-hoc comparisons of post-conditioning preferences: ** $p<0.01$, saline vs. cocaine and saline vs. LCR. Within group comparisons of pre- vs. post-conditioning preferences: @ $p<0.05$; @@ $p<0.01$.

Table 1

Characteristics of LCRs versus HCRs

Baseline	LCRs vs. HCR
Baseline Locomotor activity (novel environment)	No difference
Number of striatal DATs	LCR > HCR
In vivo striatal DA clearance (DAT activity)	No difference
Striatal extracellular DA levels	No difference
Corticosterone levels	No difference
Thigmotaxis type anxiety	No difference
NAc extracellular glutamate levels	No difference
Impulsivity ^a	LCR < HCR
Acute cocaine	
Cocaine-induced locomotor activity and rearing	LCR < HCR
Cocaine-induced freezing, head movements, and sniffing	LCR > HCR
Brain concentration of cocaine	No difference
Cocaine inhibition of striatal DA clearance (<i>in vivo</i>)	LCR < HCR
Cocaine-induced striatal extracellular DA levels	LCR < HCR
Maximal velocity of striatal [3H]DA uptake (<i>in vitro</i>)	LCR < HCR
Corticosterone levels	No difference
Thigmotaxis type anxiety	No difference
Cocaine-induced NAc extracellular glutamate levels	No difference
dSTR GluN2B ^{Y-1472} phosphorylation	LCR > HCR
Repeated cocaine	
Cocaine-induced locomotor sensitization	LCR > HCR
Number of striatal DATs	No difference
Cocaine inhibition of striatal DA clearance (<i>in vivo</i>)	No difference
Cocaine-induced striatal extracellular DA levels	No difference
Cocaine conditioned place preference	LCR > HCR
Acquisition of cocaine self-administration	No difference
Motivation to self-administer cocaine	LCR > HCR
Corticosterone levels	No difference
Thigmotaxis type anxiety	No difference
Cocaine-induced NAc extracellular glutamate levels	No difference
Discrimination of low dose cocaine ^b	LCR > HCR

^aStanis et al., 2008,^bKlein and Gulley, 2009

Table 2

Other models – Locomotor activity and cocaine self-administration

Model	HR/LR ^a	HNP/LNP ^b	ST/GT ^c	HI/LI ^d	RHA/RLA ^e	HiS/LoS ^f	bHR/bLR ^g
Locomotor activity							
<i>Novelty (novel environment)</i>	HR>LR	HNP LNP	ST: no correlation	HI LI	RHA>RLA	HiS<LoS	bHR>bLR
<i>Acute cocaine</i>	HR LR		ST<GT		RHA>RLA	HiS=LoS;	bHR=bLR
<i>Cocaine Sensitization</i>	HR>LR		ST>GT Head movement only		RHA>RLA	HiS>LoS, F only [*]	bHR>bLR Rearing only
Self-Administration							
<i>Acquisition</i>	Variable	HNP=LNP	ST GT	HI LI	RHA>RLA	HiS>LoS	bHR>bLR
<i>Maintenance</i>	HR=LR			HI=LI		HiS=LoS	bHR>bLR
<i>Escalation</i>				HI>LI (long-access)		HiS>LoS F only	
<i>Break-Point</i>	HR=LR	HNP>LNP	ST>GT	HI=LI			bHR>bLR
<i>Extinction resistance</i>		HNP>LNP	ST GT	HI>LI	RHA>RLA	HiS>LoS F only	
<i>Reinstatement</i>			ST>GT (cue, cocaine)	HI>LI (context)	RHA>RLA	HiS>LoS F only	

^{*}F = female

^aHR/LR: Belin et al., 2011; Chefer et al., 2003; Hooks et al., 1991; Mantsch et al., 2001; Marinelli and White, 2000; McCutcheon et al., 2009; Piazza et al., 2000; Sell et al., 2005

^bHNP/LNP: Beckmann et al., 2011; Belin et al., 2011

^cST/GT: Beckmann et al., 2011; Flagel et al., 2008; Robinson and Flagel, 2009; Saunders and Robinson, 2010, 2011

^dHI/LI: Anker et al., 2009; Belin et al., 2008; Broos et al., 2012; Dalley et al., 2007; Molander et al., 2011; Perry et al., 2005

^eRHA/RLA: Fattore et al., 2008; Giorgi et al., 2005; Lecca et al., 2004; Steimer et al., 1997

^fHiS/LoS: Carroll et al., 2007; Carroll et al., 2008

^gbHR/bLR: Cummings et al., 2011; Davis et al., 2008; García-Fuster et al., 2010; Stead et al., 2006

Table 3

Striatal D1 and D2 receptor binding parameters in LCRs and HCRs

dSTR				NAC			
	N	Bmax (fmol/mg protein)	Kd (nM)	N	Bmax (fmol/mg protein)	Kd (nM)	
DIRs*							
LCRs	10	1880 ± 157	1.94 ± 0.06	10	1110 ± 184	1.97 ± 0.08	
HCRs	10	1610 ± 148	2.05 ± 0.07	10	1210 ± 105	1.74 ± 0.15	
Saline	7	1980 ± 194	2.28 ± 0.24	7	1660 ± 308	2.02 ± 0.27	
	N	(fmol/mg protein)	(pM)	N	(fmol/mg protein)	(pM)	
D2Rs**							
LCRs	4	457 ± 91	47.1 ± 4.3	6	223 ± 19	48.8 ± 11.6	
HCRs	6	557 ± 74	42.2 ± 2.5	6	205 ± 22	44.0 ± 9.2	
Saline	4	540 ± 6	47.8 ± 7.5	3	242 ± 17	64.1 ± 27.5	

* DIRs measured with [³H]SCH 23390 in the presence of 100 nM ketanserin, nonspecific binding defined with 1μM SCH 39166.

** D2Rs measured with [3H]spiperone in the presence of 100 nM ketanserin, nonspecific binding defined with 10 μM raclopride.

Table 4

Baseline extracellular glutamate in NAc

	Acute cocaine			Repeated cocaine		
	Day 1	N		Day 7	N	1 week withdrawal N
HCR	7.3 ± 2.3	5		3.8 ± 0.8	7	3.8 ± 0.4 8
LCR	10.0 ± 0.7	6		2.9 ± 0.5	8	3.5 ± 0.3 8
Saline	7.9 ± 2.1	5		2.1 ± 0.5	5	4.0 ± 0.7 6

Results are expressed as mean ± SEM (pmol/sample).