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Invited review

Antecedents and consequences of drug abuse in rats selectively bred for high and low response to novelty

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ABSTRACT

Human genetic and epidemiological studies provide evidence that only a subset of individuals who experiment with potentially addictive drugs become addicts. What renders some individuals susceptible to addiction remains to be determined, but most would agree that there is no single trait underlying the disorder. However, there is evidence in humans that addiction liability has a genetic component, and that certain personality characteristics related to temperament (e.g. the sensation-seeking trait) are associated with individual differences in addiction liability. Consequently, we have used a selective breeding strategy based on locomotor response to a novel environment to generate two lines of rats with distinct behavioral characteristics. We have found that the resulting phenotypes differ on a number of neurobehavioral dimensions relevant to addiction. Relative to bred low-responder (bLR) rats, bred high-responder (bHR) rats exhibit increased exploratory behavior, are more impulsive, more aggressive, seek stimuli associated with rewards, and show a greater tendency to relapse. We therefore utilize this unique animal model to parse the genetic, neural and environmental factors that contribute to addiction liability. Our work shows that the glucocorticoid receptor (GR), dopaminergic molecules, and members of the fibroblast growth factor family are among the neurotransmitters and neuromodulators that play a role in both the initial susceptibility to addiction as well as the altered neural responses that follow chronic drug exposure. Moreover, our findings suggest that the hippocampus plays a major role in mediating vulnerability to addiction. It is hoped that this work will emphasize the importance of personalized treatment strategies and identify novel therapeutic targets for humans suffering from addictive disorders.

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1. Introduction

The United States is a world leader in drug policy agenda, yet also has among the highest levels of drug use in the world (Degenhardt et al., 2008). In particular, the US is an extreme outlier when it comes to cocaine use, with an estimated 16% of the population reporting lifetime use, compared to just 4.3% in the world's second leading nation in cocaine use (Degenhardt et al., 2008). High rates of experimentation with drugs lead to higher rates of dependence. Approximately 8.4% of the population, or 25 million Americans, aged 12 or older, meet criteria for substance abuse, including illicit drugs and alcohol (SAMHSA, 2010/2011). These statistics beg the following questions: Why do people experiment with these potentially addictive drugs in spite of numerous anti-drug campaigns? Why are some people able to stop taking drugs while others become addicted? There is obviously not a simple answer to these questions, but gaining a better understanding of the antecedents that contribute to that initial drug-taking experience and the consequences that follow is critical for the successful treatment of addiction. Here we will briefly review some of the human literature that has identified particular personality traits or temperaments that are associated with addiction vulnerability, and the remainder of the article will be centered on animal models that capture some of these traits. In particular, we will focus on rats that

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have been selectively bred in our laboratory and represent a unique genetic animal model of individual differences in addiction liability, allowing us to examine the neurobiological antecedents and consequences of drug abuse.

2. Individual differences in addiction liability in humans

There is no doubt that vulnerability to substance abuse is multifaceted, consisting of environmental, genetic and neural elements. The complex interactions among these dimensions make it especially difficult to isolate a single factor that drives the maladaptive tendencies constitutive of addiction. More than four decades ago, a number of biologically based personality theories began to emerge, proposing that traditional personality phenotypes were comprised of multiple interactive dimensions (Gray, 1970; Eysenck and Eysenck, 1985; Cloninger, 1986, 1989). These theories introduced behavioral constructs that were later shown to be relevant to individual differences in addiction liability (e.g. see Ersche et al., 2010). Collectively, these traits all fall within the broader concept of "behavioral disinhibition", and include impulsivity (Eysenck and Eysenck, 1964; Acton, 2003), behavioral approach (Gray, 1970, 1987), and perhaps most prominently, "novelty-seeking" (Cloninger, 1986) and "sensation-seeking" (Zuckerman and Cloninger, 1996; Zuckerman and Kuhlman, 2000). These traits can each be measured with different instruments, yet are highly overlapping conceptually and highly correlated empirically (Zuckerman and Cloninger, 1996). High novelty/sensation-seeking scores correlate with "impulsiveness" and "exploratory excitability" (Cloninger, 1987; Svrakic et al., 1993), as impulsive individuals are thought to gravitate to novel and risky situations and show less anxiety about them (Hiroi and Agatsuma, 2005). These combined traits lead an individual to rapidly respond to cues for rewards despite potential punishment (Zuckerman and Kuhlman, 2000), a hallmark of addictive behavior. Further, there is evidence linking such traits expressed early in childhood to the development of addiction in adulthood (e.g. Masse and Tremblay, 1997; Ayduk et al., 2000; Eigsti et al., 2006).

One of the most compelling studies correlating a formal measure of novelty-seeking with propensity to substance abuse in humans involved a total of 7588 individual twins (Khan et al., 2005). While the study was focused on co-morbidity of various disorders, it also reported the relationship between particular personality traits and specific disorders, including substance abuse. Unlike neuroticism, increased novelty-seeking was not a broad predictor of all psychiatric disorders. However, high novelty-seeking was highly predictive of "externalizing disorders" including alcohol and drug dependence. Individuals with externalizing disorders are characteristically aggressive and impulsive and more likely to show drug-seeking and psychopathic behavior. By contrast, individuals prone to "internalizing disorders" are more likely to exhibit anxiety, depression and other mood disorders following psychosocial stress. However, there is also ample evidence of co-morbidity between substance abuse and severe mood disorders, suggesting that internalizing disorders do not protect against, but rather may also predispose toward, addictive behavior. Indeed, it has been estimated that close to 25% of individuals with a mood disorder, and 40% of individuals with bipolar disorder, self-medicate with an addictive substance to cope with their symptoms (Bolton et al., 2009). Finally, while drug abuse can be triggered by stressful social events, it can in itself become a source of stigma, extreme marginalization and further social stress (Kreek, 2011), creating a vicious cycle of social stress, negative affect and substance abuse. This then suggests that both extremes of emotional reactivity, leading to either internalizing or externalizing psychopathologies, can be vulnerability factors to addiction.

Human studies also strongly suggest that the propensity to abuse drugs is heritable, sometimes as a general tendency and sometimes for particular drugs (Nielsen et al., 2010). An example of this literature can be found in the work of Hicks et al. (2004) using over 500 families from the Minnesota Twin Family Study, which showed a highly heritable vulnerability for "behavioral undercontrol" or "disinhibitory syndromes", including drug dependence. Thus, in humans, the propensity for substance abuse appears to arise in part from genetic vulnerability that manifests in certain temperaments with high reactivity to environmental stimuli and/or strong responsiveness to psychosocial stress. Against such a genetic background, developmental events and stressful environmental challenges in adulthood can conspire to lead to maladaptive coping strategies such as drug-seeking behavior and addiction (for review see Enoch, 2012).

Taken together, this body of work provides good evidence for a relationship between certain personality traits and drug abuse in humans, but it does not establish causality. Novelty-seeking and related traits might increase the odds of being prone to experimenting with drugs in some individuals. Severe vulnerability to psychosocial stress may lead others to self-medication with drugs of abuse. But questions remain as to the neurobiological mechanisms underlying this increased vulnerability and the determinants of the transition to addiction. A fundamental understanding of the underlying biology is necessary in order to devise strategies that are better tailored to treat and prevent addiction in individuals with differing types of vulnerabilities. Addressing these questions requires the use of animal models that capture some of these temperamental features and reflect individual differences in addiction liability.

3. Animal models of individual differences in addiction liability

While human genetic and epidemiological data lend strong support to the notion that individuals differ in susceptibility to addiction, only in recent years has this issue been seriously considered as a potential avenue of therapeutic value (e.g. Ersche et al., 2012b; Tarter et al., 2012) and gained increasing momentum in the preclinical literature (Saunders and Robinson, 2011; Dalley et al., 2007; Belin et al., 2009; Flagel et al., 2009). The first animal model characterizing individual differences in addiction liability was introduced over two decades ago (Piazza et al., 1989); yet, surprisingly few models have since emerged. In their seminal paper, Piazza and colleagues demonstrated that, like humans, only some rats readily self-administer drugs of abuse. This tendency to take drugs could be predicted by individual differences in response to a novel environment or by a pharmacological challenge with psychostimulants. That is, high-responder (HR) rats, or those with increased rates of exploratory activity in an inescapable novel environment, exhibit higher levels of amphetamine-induced locomotor activity and acquire self-administration of this drug at lower doses than low-responder (LR) rats, or those with low levels of activity in an inescapable novel environment (Piazza et al., 1989). HRs and LRs have since been shown to differ in the acquisition of self-administration for other drugs of abuse including cocaine (Marinelli and White, 2000; Piazza et al., 2000), nicotine (Suto et al., 2001), morphine (Ambrosio et al., 1995), and ethanol (Nadal et al., 2002); and show dose-dependent differences in behavior during extended access (i.e. 10-h daily sessions) self-administration procedures (Mantsch et al., 2001).

HR rats also characteristically exhibit an increased and prolonged corticosterone response to the mild stress of novelty (Piazza et al., 1989, 1996) and exhibit greater stress-induced elevations in mesolimbic dopamine activity relative to LR rats (Dellu et al., 1996).

This suggests that HR rats are not insensitive to environmental stressors, but rather that mild stress is not sufficient to inhibit their exploratory behavior, and may in fact promote that behavior.

While these HR/LR differences exist basally or following mild stress, exposure to repeated stress (Kabbaj et al., 2001) or repeated administration of amphetamine (Piazza et al., 1989) or corticosterone (Piazza et al., 1991) serve to eliminate individual differences in drug self-administration behavior, causing LR rats to behave similarly to HR rats. Indeed, while "novelty-seeking" serves as one path to vulnerability to substance use, social stress appears to represent an alternate path. Thus, following repeated social defeat, LR animals, which are not typically prone to drug seeking, become as willing to self-administer cocaine as HR animals (Kabbaj et al., 2001). This may resemble the "self-medication" path to drug-seeking observed in depressed humans. As will be discussed below, rats genetically bred for the LR phenotype are particularly prone to "anhedonia" following stress (Calvo et al., 2011; Stedenfeld et al., 2011), and the availability of psychostimulants may represent a compensatory response. Thus, the HR/LR animal model highlights behavioral, environmental and neurobiological factors that might differentially predispose an individual to drug seeking behavior.

While willingness to experiment with drugs represents the first element of vulnerability to substance abuse, an additional critical variable is conversion from initial drug taking to addictive behavior. Piazza and colleagues (Deroche-Gamonet et al., 2004) demonstrated that diagnostic criteria for addiction could also be modeled in rats. Following protracted exposure to cocaine self-administration rats will show, 1) difficulty stopping drug use or limiting intake, 2) increased motivation for the drug, and 3) continued drug-taking behavior in the face of adverse consequences. Importantly, despite equal cocaine intake, only 17% of the animals met all three criteria for addiction and 41% appeared resilient (i.e. 0 criteria), further highlighting individual differences in vulnerability (Deroche-Gamonet et al., 2004). It is important to note that in this study the development of addiction was not predicted by locomotor response to novelty, the trait previously associated with the propensity to acquire initial drug-taking behavior (Piazza et al., 1989). This paper introduced an animal model that captures multiple features of human addiction and redefined "addiction" in the pre-clinical literature, changing the focus from the initiation of drug self-administration to compulsive drug use.

With the advent of this animal model and ability to distinguish between the initial propensity to use drugs and the transition to addiction, pre-clinical researchers have begun to parse which behavioral traits actually contribute to individual differences in vulnerability to addiction (for review see Belin and Deroche-Gamonet, 2012). While the strongest evidence in the human literature centers around impulsivity and novelty/sensation-seeking, it remains a matter of debate as to which trait might be the best predictor of the transition to addiction (e.g. Ersche et al., 2010;, 2012a, 2012b). It should also be noted that impulsivity and novelty/sensation-seeking are multidimensional constructs and it is questionable which facets of these human traits we are able to capture in animal models. Nonetheless, a number of recent studies in the pre-clinical literature suggest that these traits are distinct and dissociable in terms of relevance to addiction liability.

Locomotor response to an inescapable novel environment, as described by Piazza et al. (1989), is considered to reflect "sensation-seeking" and remains a good predictor of the initial propensity to take drugs (e.g. Klebaur et al., 2001; Cain et al., 2005; Belin et al., 2008), but is not associated with addiction liability *per se* (Deroche-Gamonet et al., 2004; Belin et al., 2008). In contrast, "novelty-seeking" behavior, as indicated by preference for a novel environment in a free choice situation (i.e. novelty-induced conditioned place preference, Hughes, 1968), does not predict the acquisition of drug-taking behavior, but does predict the propensity to compulsive cocaine use and severity of addiction-like behavior (Belin et al., 2011). Similarly, it has been shown that relative to low-impulsive rats, high-impulsive rats, as defined by their ability to withhold inappropriate responding in a five-choice serial reaction time test (5-CSRTT), do not differ in their initial acquisition of drug-taking behavior, but this measure of impulsivity does predict the switch to compulsive cocaine self-administration following prolonged exposure to the drug (Belin et al., 2008). Interestingly, this measure of impulsivity appears to be orthogonal to both sensation- and novelty-seeking behavior, yet, high-impulsive rats display a higher novelty-preference relative to low-impulsive rats, suggesting that these two behavioral traits (i.e. impulsivity and novelty-seeking), may interact to increase individual vulnerability to compulsive cocaine use (Belin and Deroche-Gamonet, 2012). Indeed, we believe that there is not a single trait, but rather, a constellation of traits that renders one more susceptible to addiction.

The pre-clinical data in conjunction with the human literature described above highlight the complexity of the factors that contribute to addiction liability and emphasize the importance of studying individual differences. Here we will describe a selectively bred animal model of individual differences in response to environmental stimuli and associated differences in emotional reactivity. This model captures a number of neurobehavioral dimensions of relevance to addiction and thereby allows us to investigate the antecedents and consequences of drug abuse vulnerability by linking genetic, neural and behavioral elements.

4. Selectively bred high- and low-responder rats

From an adaptive standpoint, it is reasonable to hypothesize that it is advantageous for some members of a population to be risk-taking and willing to actively explore the environment in search of food, mates and other resources; while others are more conservative and guarded, protecting themselves and their progeny against potential threats. In fact, in outbred rodent populations there is a normal distribution of this trait. However, we and others (see Marinelli, 2005) have noted significant batch-to-batch variation in the HR and LR traits in outbred populations and it has been difficult to determine whether or not the "sensation-seeking" trait is stable or state dependent in these populations. Thus, if we were to discover the genetic and neural causes that lead to vulnerability to drug-seeking behavior, it was important to identify the antecedent variables that determine these traits. It was therefore critical to generate a model that would allow us an *a priori* way of predicting which animals were destined to become high- vs. low-responders and to determine whether various interventions could alter their phenotypes.

Thus, almost a decade ago, we embarked on a selective breeding paradigm to enrich for the HR and LR traits in rats, modeling those that explore the most and the least, respectively, in a novel environment. An extensive set of behavioral characterizations, as outlined below, has indicated that environmental exploration, the trait on which these animals were bred, is a fundamental feature of the way an individual reacts with the world, copes with stress, expresses emotions, makes associations and responds to addictive drugs.

4.1. Breeding for "sensation-seeking"

The founding population of our bred high-responder (bHR) and bred low-responder (bLR) rat lines was comprised of 60 male–female pairs of adult Sprague-Dawley rats purchased from three

different breeding colonies at Charles River Laboratories (Kingston, NY, USA; Portage, MI, USA; Saint-Constant, QC, Canada). Rats were tested for locomotor response to an inescapable novel environment (acrylic cage, 43 × 21.5 × 24.5 cm), and locomotor scores were determined by summing horizontal and rearing activity during the first hour of testing. Males and females with the top and bottom 20% of locomotor scores were selected for breeding. A number of measures were taken to maximize genetic variation and to minimize inbreeding (see Stead et al., 2006). First, sib-matings were avoided in the founding population by only breeding pairs of animals derived from different colonies. Second, for each generation, 12 litters were maintained for each of the lines. Finally, the selection of breeding pairs consistently followed a rigid system of within-family selection and cyclical outbreeding (Falconer and Mackay, 1996). Thus, only the single "best" male and female from each litter are selected to propagate the lines. To date, we have bred over 35 generations of the bHR/bLR lines. We have compared the bHR/bLR lines to cross-bred animals that are generated by breeding bHR animals with bLR animals, and we consistently find that the cross-bred animals fall intermediate to the extremes in terms of locomotor response to novelty and anxiety-like behavior (Fig. 1). The same is true when the bred lines are compared to commercially purchased outbred rats. Thus, bHRs and bLRs make up the top and bottom few percent of the normal distribution of the trait on which they were selected. Moreover, we can predict with ~99% certainty the behavioral phenotype based on lineage, allowing us to investigate developmental factors that contribute to these phenotypes. We have found that bHRs and bLRs exhibit all of the key features of the outbred HR/LR rats, but also show some additional and distinctive characteristics that are highly stable across generations (Fig. 2, Table 1). Indeed, we seem to have co-selected for a number of traits that are not necessarily reflected in outbred HR/LR rats, but that seem to be especially relevant to addiction. More broadly, as described below, the complex of traits appear to be characteristic of an "externalizing" propensity for the bHRs and an "internalizing" propensity for the bred LRs.

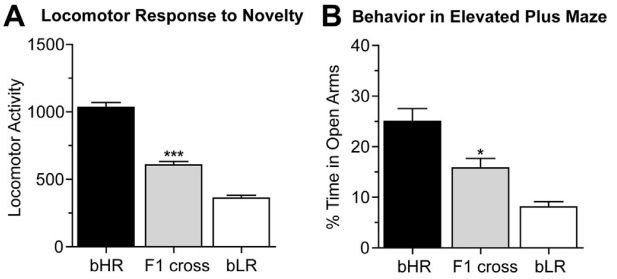

Fig. 1. Cross-breeding bHR and bLR rats produces an intermediate behavioral phenotype. (A) Locomotor response to novelty and (B) anxiety-like behavior in the elevated plus maze (EPM) were assessed in male rats bred for high (bHR) versus low (bLR) locomotor response to novelty and offspring produced by cross-breeding the bHR and bLR lines. The cross-bred progeny (F1 Cross) represent the first generation derived from breeding a bHR male/bLR female or bHR female/bLR male. (A) Novelty-induced locomotor activity was assessed by quantifying the number of beam breaks in a novel test chamber during a 1-h test. bHR rats exhibited the highest level of locomotor activity, bLR rats exhibited very low levels of activity, while the F1 Cross rats showed an intermediate level of activity in the novel environment (A) which was significantly different from both bHR and bLR rats (***$p < 0.001$). (B) Anxiety-like behavior was assessed by determining the percentage of time spent in the open arms of an EPM during a 5-min test. bHR rats showed the lowest levels of anxiety behavior on the EPM, spending more time in the open arms compared to all other groups. bLR rats spent the least amount of time in the open arms compared to the other groups, and the F1 Cross rats exhibited an intermediate phenotype (*$p < 0.05$). Taken together, these results provide further evidence for a genetic basis of the bHR/bLR behavioral phenotypes. Data are means ± SEM; groups were compared by 1-way ANOVA followed by Tukey's post-hoc tests as necessary. n/group = 63–69 in A and 30–33 in B.

4.2. "Novelty-seeking" vs. "sensation-seeking" behavior

Given the recent literature emphasizing the distinction between "novelty-seeking" and "sensation-seeking" in animal models of addiction (for review see Belin and Deroche-Gamonet, 2012; Bardo et al., 2013), it should be noted that we currently have no evidence to suggest that bHRs and bLRs differ in "novelty-seeking" behavior. Thus, when given the free choice to explore a novel vs. familiar environment, there is no difference in preference between the phenotypes (Lee et al., 2011). Although bHRs exhibit increased activity in both sides of the testing chamber relative to bLRs, the amount of time spent in either the familiar or novel side does not differ. In fact, much to our surprise, both bHRs and bLRs preferred the novel side of the test chamber over the familiar side. Further, we did not detect pronounced differences in corticosterone response to the novelty-seeking test in the bred lines. These data are consistent with the literature in outbred animals which suggests that the "sensation-seeking" vs. "novelty-seeking" traits are indeed dissociable (Cain et al., 2005; Belin et al., 2011; but see Dellu et al., 1996) and that the two measures elicit different levels of stress response (Misslin et al., 1982) and are likely mediated by different neurobiological systems (for review see Bardo et al., 2013). In contrast to the data in outbred animals, however, we would argue that the "novelty-seeking" trait is not a required predictor of addiction liability in the selectively bred lines, while the "sensation-seeking" trait, which is the basis of our breeding strategy, is indeed predictive.

4.3. Learned behavior

The selectively bred rat lines were selected for differences in locomotor response to a novel environment; yet, we see pronounced differences on a range of behavioral tasks. It could be argued that a number of these behavioral outcomes are driven by inherent differences in activity as well as learning ability, or perhaps an interaction of the two. It should be noted, however, that: 1) bHR and bLR animals do not differ in homecage locomotion during the light phase of their circadian cycle (Kerman et al., 2012), the time at which they are typically tested on behavioral measures, and 2) we have not observed pronounced differences in learning ability between the two lines. As mentioned below, we see similar rates of learning on measures of classical conditioning (Flagel et al., 2010b) and in operant learning, given the appropriate conditions (Flagel et al., 2010a). Further, bHRs and bLRs do not differ in the learning of a Morris Water Maze task or in a novel odor recognition task (Clinton et al., unpublished data). Thus, while there are likely a number of factors contributing to the behavioral phenotypes of bHRs and bLRs, we do not believe underlying differences in learning ability are driving the distinctions between the two.

4.4. Anxiety-like behavior

Beyond its direct relevance to substance abuse, the HR/LR trait correlates with stress-reactivity, spontaneous anxiety-like behaviors and other measures of "emotionality" in both outbred and selectively bred populations. In general, LR rats are considered more anxious than HR rats (Dellu et al., 1996; Kabbaj et al., 2000; Calvo et al., 2011), and we have consistently shown a similar pattern in our bred lines. Thus, bLR rats spend less time in the anxiogenic portions (i.e. open or brightly lit areas) of the elevated plus maze, light–dark box and open field apparatus (Stead et al., 2006). Interestingly, it has been shown in both outbred and selectively bred animals that exposure to the mild stress of a novel environment elicits an increased and prolonged secretion of corticosterone in HR rats relative to LR rats (Dellu et al., 1996; Kabbaj et al., 2000;

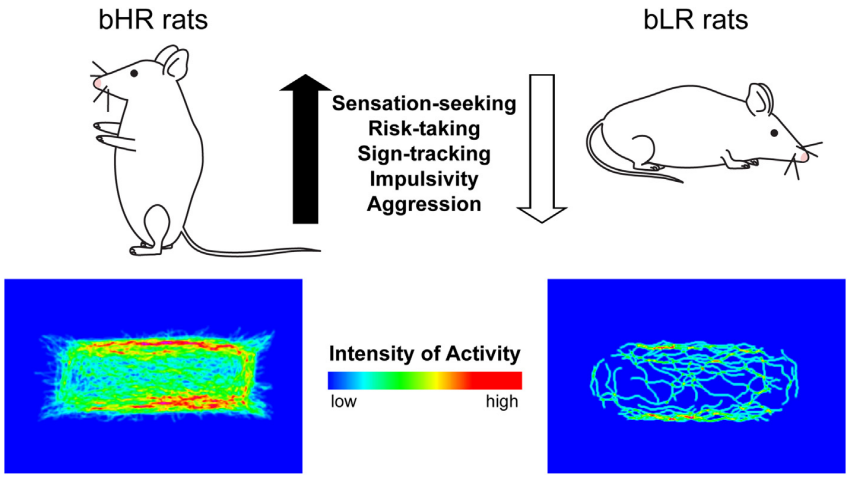

Fig. 2. Addiction-related traits in selectively-bred high (bHR) and low (bLR) responder rats. bHRs exhibit increased sensation-seeking and risk-taking behavior, an increased propensity to sign-track, are more impulsive and more aggressive relative to bLR rats. Differences in activity during a 2-h exposure to a novel environment were visually examined using activity maps (Clever Sys., Inc.) that illustrate both the pattern and intensity of activity. Representative activity maps from a bHR (left) and bLR (right) rat from the 27th generation of our selective breeding colony illustrate that locomotor activity in a novel environment was greatly enhanced in bHR rats compared to bLRs.

Clinton et al., 2008). These HR/LR differences in hypothalamic–pituitary–adrenal (HPA) axis reactivity may seem counterintuitive given their respective displays of "anxiety-like" behavior, but it has been suggested that HR rats take risks and seek novel or "stressful" situations for the reinforcing properties of corticosterone. In fact, it has been shown that outbred HR rats will self-administer corticosterone at lower doses than LR rats, suggesting they are more sensitive to the reinforcing properties of this stress hormone (Piazza et al., 1993). Thus, it seems reasonable to speculate that bHR rats do not necessarily find these environmental challenges less stressful *per se,* but perhaps more rewarding, akin to human sensation-seekers.

4.5. Sign- and goal-tracking behavior

We have also found that bHRs and bLRs respond quite differently to environmental stimuli associated with reward (Flagel et al., 2010b, 2011). When exposed to a Pavlovian conditioning paradigm wherein the brief (8-sec) presentation of an illuminated lever (conditioned stimulus, CS) is paired with a food reward (unconditioned stimulus, US), two very distinct conditioned responses emerge. bHRs exhibit a sign-tracking response which consists of approach toward and manipulation of the lever-CS upon its presentation. In contrast, bLRs develop a goal-tracking response such that when the lever-CS is presented they go to the receptacle where the food reward will be delivered upon lever-CS retraction. It should be noted that no response is required in order to receive the food reward and that both phenotypes typically retrieve all of the pellets delivered. Twenty-five trials of lever-food presentation occur in a given session, and we see robust differences emerge between the phenotypes by the second conditioning session (Flagel et al., 2010b). It is also important to note that both phenotypes show evidence of having learned their respective conditioned responses (Flagel et al., 2010b, 2011). That is, over time, the probability of approach to the lever-CS for bHRs and to the food receptacle for bLRs increases at the same rate, and the latency with which they do so decreases. Thus, these robust phenotypic effects do not appear simply to be a byproduct of differences in activity or learning ability. Rather, they reflect differences in the attribution of incentive motivational value to reward cues (Flagel et al., 2009; Robinson and Flagel, 2009).

It is believed that reward-related cues acquire the ability to control behavior in part because they attain incentive motivational properties through Pavlovian learning, and cues associated with drugs may be attributed with pathological levels of incentive salience (Stewart et al., 1984; Robinson and Berridge, 1993; Tomie, 1996; Everitt et al., 2001). Indeed, it has been demonstrated that a cocaine-associated cue is more effective in maintaining self-administration behavior, and instigates more robust relapse behavior in sign-trackers than goal-trackers, and this is true in both outbred (Saunders and Robinson, 2010, 2011) and selectively bred animals (Flagel et al., 2010a). Further, we have shown that bHRs, but not bLRs approach a discrete Pavlovian cue associated with cocaine delivery (Flagel et al., 2010b). Thus, bHRs attribute excessive incentive salience to cues that predict food or drug reward, and for them the cue itself becomes a reinforcer (Flagel et al., 2011). In contrast, bLRs use cues merely as predictors of reward. These distinct conditioned responses are accompanied by striking

Table 1
Summary of behavioral phenotypes. This table provides a summary of differences in addiction-related behaviors in selectively bred high-responder (bHR) vs. bred low-responder (bLR) rats with associated primary references. DRL, differential rates of low reinforcement.

Behavior	Phenotype differences	Primary reference
Sensation-seeking	bHR > bLR	Stead et al., 2006
Risk-taking		Stead et al., 2006
- Elevated plus maze	bHR > bLR	
- Light–dark box	bHR > bLR	
- Open field	bHR > bLR	
Response to cocaine		Clinton et al., 2012
- Acute	bHR > bLR	
- Sensitization	bHR > bLR	
Acquisition of drug-taking	bHR > bLR	Davis et al., 2008
Response to reward cues		Flagel et al., 2010b
- Sign-tracking	bHR > bLR	
- Goal-tracking	bHR < bLR	
Impulsivity		Flagel et al., 2010b
- Delayed reinforcement	bHR < bLR	
- Probabilistic choice	bHR = bLR	
- DRL	bHR > bLR	
Aggression	bHR > bLR	Kerman et al., 2011

differences in the dopamine response, and we have found that the sign-tracking response of bHRs is dopamine-dependent, whereas the goal-tracking response of bLRs is not (Flagel et al., 2011).

The sign-tracking and goal-tracking phenotypes have been remarkably stable across generations of the bred lines. Similar to locomotor response to novelty, the trait for which these lines were selected, we can predict with ~99% accuracy whether an individual rat will be a sign-tracker or a goal-tracker. These findings are especially interesting because in outbred rats, locomotor response to novelty and the tendency to sign-track or goal-track are not correlated (Robinson and Flagel, 2009), suggesting that these two traits may be dissociable. Nevertheless, it appears that the sign-tracker/goal-tracker trait was co-selected over the course of breeding for locomotor response to novelty. To determine the extent to which these traits are genetically related will require additional studies, for example, the generation of replicate lines.

4.6. Impulsive behavior

It has been suggested that sign-tracking behavior may be reflective of a lack of inhibitory control over behavior, which is one attribute of impulsivity. 'Impulsivity', however, is a multidimensional construct. There are several forms of so-called impulsive behavior and it is questionable whether – or which – animal models are translatable to humans (Evenden, 1999; Chamberlain and Sahakian, 2007). Nonetheless, two facets of impulsivity in particular have been the focus of preclinical substance abuse research, 'impulsive choice' and 'impulsive action' (Olmstead, 2006; Perry and Carroll, 2008). Impulsive choice paradigms include delay-discounting procedures and probabilistic-choice or risk-based decision making tasks. Impulsive action assesses the ability to withhold responding, or impaired inhibition, and can be assessed using a differential rates of low reinforcement (DRL) task.

When given the choice on a delay-discounting task, bHRs choose a larger delayed reward, and do so significantly more often than bLRs. These data suggest that bHRs are *less impulsive* than bLRs, but an alternative interpretation is that bHRs exhibit a preference for the larger delayed reward because the incentive value of the reward is disproportionately enhanced relative to the small reward (Flagel et al., 2010b). Interestingly, on a probabilistic choice task, where the choice was between a small reward delivered 100% of the time vs. a larger probabilistic reward, the phenotypes performed almost identically. In contrast, when impulsive action was assessed, we found that bHRs were *more impulsive* – they were less able to withhold responding in order to receive a reward on a DRL task. These results support those of Stoffel and Cunningham (2008) in outbred HR/LR rats and are also consistent with the fact that outbred sign-tracking rats show deficits on measures of impulsive action, but not impulsive choice (Lovic et al., 2011). However, these data seem to be incongruent with those of Belin et al. (2008), who concluded that impulsive behavior is not associated with the "sensation-seeking" trait, and that it is impulsivity rather than reactivity to a novel environment that is most relevant to compulsive drug use. It should be noted that the measure of impulsivity used in the Belin et al. (2008) study differs from those that we used. Namely, Belin et al. (2008) characterized animals as high- vs. low-impulsivity based on performance in a five-choice serial reaction-time task (5-CSRTT), which is considered to reflect sustained visual attention as well as impulsivity (Robbins, 2002). Nonetheless, based on these studies, we concluded that, at least in the selectively bred rat lines, there seems to be a strong association between locomotor response to novelty, the propensity to attribute incentive motivational value to reward cues, and impulsivity as measured by impaired inhibition (Flagel et al., 2010b).

4.7. Aggressive behavior

Aggression is another behavioral trait that falls under the category of "behavioral disinhibition" and has been associated with impulsivity, risk-taking behavior and substance abuse (Martin et al., 1994; Moeller et al., 1994; Brady et al., 1998; Ball, 2005). We assessed aggressive behavior in the bred lines using a resident-intruder paradigm (e.g. van Erp and Miczek, 2007; de Almeida et al., 2008) which is known to elicit aggressive behavior as well as fear and anxiety responses (for review see Martinez et al., 1998; Buwalda et al., 2005). Male bHR or bLR rats were housed with a female mating partner for 2 weeks, and on the test day, the female partner was removed and each resident male was presented with an intruder male rat for a 10-min period. Compared to bLRs, bHR resident rats exhibited increased aggression when faced with an intruder and associated increases in intruder-induced corticosterone and testosterone secretion (Kerman et al., 2011).

4.8. Response to cocaine and drug-taking/seeking behaviors

Similar to outbred HR/LR rats, we have shown that the bred lines differ in their psychomotor response to cocaine and in the acquisition of drug-taking behavior. We have found repeatedly, across generations, that bHRs exhibit an enhanced acute and sensitized locomotor response to cocaine treatment relative to bLRs (Garcia-Fuster et al., 2010; Clinton et al., 2012). These effects were evident following administration of 15 mg/kg of cocaine (i.p.) for 7 days, with the behavioral response assessed on days 1 and 7 of treatment and then following 14 days of abstinence (Garcia-Fuster et al., 2010). Interestingly, rearing activity seemed to be the primary form of locomotion contributing to these differences. However, using a slightly different paradigm which incorporates dose-effect analyses (7.5, 15, 30 mg/kg cocaine; Flagel and Robinson, 2007), we have found that bHRs exhibit more stereotyped head movements, with a leftward and vertical shift in the dose–response function on both the first and last days of treatment relative to bLRs (Waselus et al., 2009). Thus, these cocaine-induced phenotypic differences go beyond distinct patterns of ambulatory activity.

Like their outbred counterparts, bHRs acquire cocaine self-administration significantly faster than bLRs (Davis et al., 2008; Cummings et al., 2011). This is true for both males and females, but there are profound sex differences such that female bHRs self-administer more cocaine than bHR males and bLRs of both sexes (Davis et al., 2008; Cummings et al., 2011). These phenotype- and sex-dependent differences in acquisition of self-administration were apparent with 2 or 3 h of daily access to cocaine, and we have not yet examined differences between the bred lines under extended access conditions (Ahmed and Koob, 1998). Importantly, however, we have shown that when we control for the amount of drug intake, bHRs and bLRs learn to self-administer cocaine equally well, and the phenotypic differences that exist during the early acquisition phases are due to the rate of drug intake, not learning ability (Flagel et al., 2010a).

Relative to bLRs, bHRs also exhibit increased motivation for cocaine, as measured by breakpoint on a progressive ratio schedule of reinforcement (Cummings et al., 2011). This pattern of responding is true of both male and female rats, but the phenotypic differences can be eliminated with higher doses of the drug in female bred rats, but not males (Cummings et al., 2011). Studies in outbred rats support the notion that HRs are willing to work harder to obtain drug rewards than LRs (Grimm and See, 1997; Suto et al., 2001). Thus, our data in the bred lines is consistent with that in outbred animals, demonstrating that locomotor response to a novel environment predicts response to psychostimulants, acquisition of

drug-taking behavior and possibly motivation for the drug. However, some of our more recent findings suggest that bHRs and bLRs also differ on measures indicative of "addiction", which is in contrast to reports in outbred animals (Deroche-Gamonet et al., 2004; Belin et al., 2008, 2011). Using methodology similar to that used by Deroche-Gamonet et al. (2004), we have found that after prolonged drug-taking experience bHRs, but not bLRs, begin to seek the drug when it is no longer available (Flagel et al., 2010a). That is, bHRs exhibit persistence in drug-seeking behavior, or difficulty stopping use. bHRs also show enhanced drug- and cue-induced reinstatement following 1 week, and 1 month of abstinence, respectively (Flagel et al., 2010a).

Taken together, we have found there to be robust differences between bHRs and bLRs on a number of traits relevant to addiction, including sensation-seeking, anxiety-like behavior, impulsivity, aggression, response to reward cues and drug-seeking behavior. Relative to bLRs, bHRs are "behaviorally disinhibited" and represent those individuals at one extreme of the population that may be highly susceptible to addiction. Using this unique genetic animal model that captures individual differences in addiction liability, we have begun to uncover some of the neurobiological antecedents and consequences of drug abuse.

5. Neuromolecular antecedents and consequences of addiction liability

A number of studies, both pre-clinical and clinical, have examined the neurobiological consequences of drug abuse, including the differential responses between individuals (e.g. McCutcheon et al., 2009; Ersche et al., 2011; Gould et al., 2012; Sweitzer et al., 2012). It has remained difficult, however, to determine whether the same differences existed prior to drug exposure and contributed to vulnerability to drug-seeking and addiction, or if these differences resulted from the impact of the drugs on the brain. The availability of selectively bred lines where drug abuse liability could be determined *a priori*, including in early development, has allowed us to address these questions. In general, it is clear that numerous differences exist basally (Turner et al., 2008; Garcia-Fuster et al., 2009; Flagel et al., 2010b; Kerman et al., 2011; Garcia-Fuster et al., 2012; Kerman et al., 2012), many of which likely contribute to differences in the drug-seeking behavior or the conversion to addiction. Some of the same molecules that modify initial vulnerability are also impacted by chronic drug use, representing both antecedents and consequences of substance abuse, as discussed below (see also Fig. 3). In general, differences in gene expression are temporarily

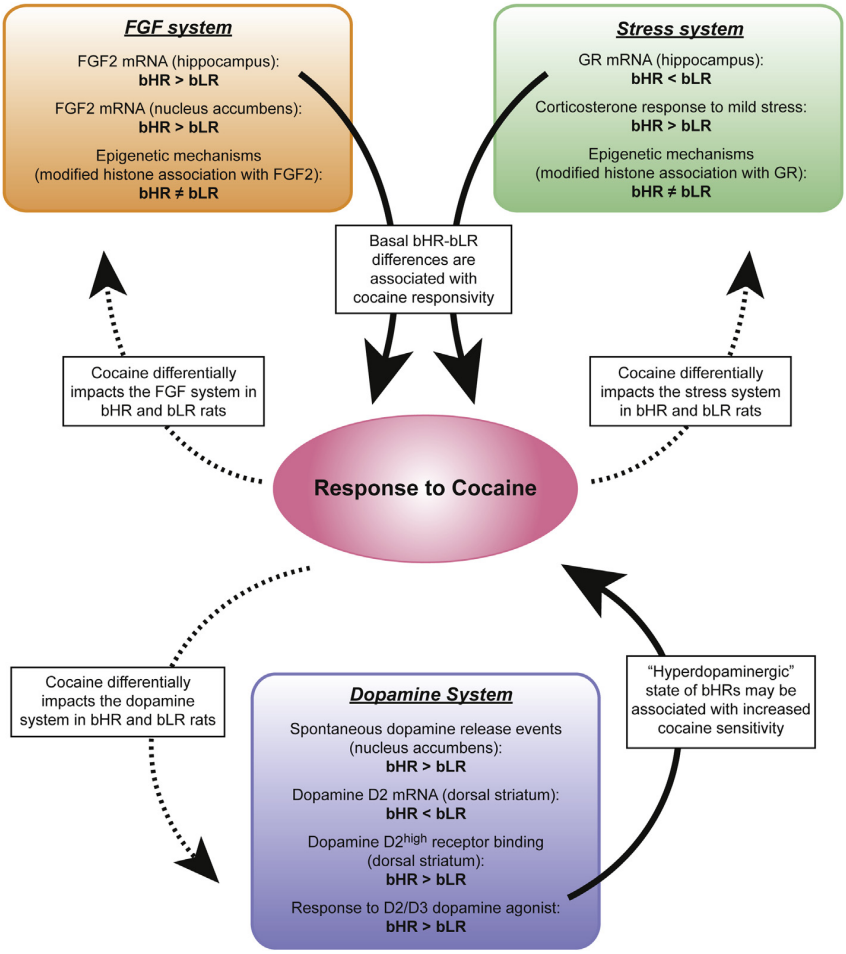

Fig. 3. Neurobiological antecedents and consequences of drug abuse in selectively-bred high (bHR) and low (bLR) responder rats. Many of the same molecules that modify initial vulnerability to addiction (solid arrows) are also impacted by repeated exposure to cocaine (dashed-line arrows). Basal differences between bHR and bLR rats in the FGF (orange), stress (green), and dopamine (purple) systems have been identified in discrete brain regions. The data following cocaine exposure are indicative of phenotype-specific alterations that are distinct from differences under basal conditions.

erased immediately following exposure to chronic drugs, as the drug itself is a dominant, unifying factor. However, after a period of abstinence, new gene expression differences emerge and are more profound and extensive than at baseline (Capriles et al., and Waselus et al., unpublished data). This suggests that in order to understand the long-term consequences of drugs of abuse and the propensity for relapse, it is important to define both the molecular and genetic antecedents as well as the consequences of the drug exposure on the brains of different individuals. Below we provide some examples of molecular mechanisms that exhibit basal and/or post drug differences as a function of the HR/LR trait.

5.1. Stress system

In their original paper describing the HR/LR model, Piazza et al. (1989) speculated that differences in response to stress underlie the behavioral phenotypes. A number of studies have since demonstrated that HRs exhibit increased stress-induced corticosterone levels relative to LRs following mild, but not severe, stressors (Dellu et al., 1996; Kabbaj et al., 2000). The increased corticosterone response in HR rats is thought to reflect impaired negative feedback of the hypothalamic-pituitary-adrenal (HPA) axis, which is likely driven by lower levels of glucocorticoid receptor (GR) expression in HRs relative to LRs (Kabbaj et al., 2000). The low levels of hippocampal GR expression in HRs also appear responsible, at least in part, for their behavioral phenotype, as administration of a GR antagonist (RU38486) into the hippocampus increases exploratory behavior and decreases anxiety-like behavior in LRs, rendering the two phenotypes indistinguishable (Kabbaj et al., 2000). The notion that elevation in hippocampal GR can enhance anxiety-like behavior is further supported by our work in transgenic mice demonstrating that overexpression of GR in the forebrain, particularly in hippocampus, leads to increased anxiety behavior (Wei et al., 2004). Interestingly, this phenotype is strongly dependent on early development, as GR overexpression prior to weaning is necessary and sufficient for increased vulnerability to both anxiety and drugs of abuse in adulthood (Wei et al., 2012).

Like outbred HR rats, bHRs exhibit lower basal levels of hippocampal GR mRNA along with an increased and prolonged corticosterone secretion in response to mild stress (Clinton et al., 2008). Further, we recently found basal phenotypic differences in the association of modified histones with GR, suggesting that epigenetic mechanisms may be responsible for the lower levels of GR mRNA in bHRs (Chaudhury et al., unpublished data). In addition, preliminary data suggests that there are cocaine-induced differences in GR mRNA expression in the hippocampus of bHRs vs. bLRs following prolonged abstinence (Waselus et al., unpublished data). Taken together, these data suggest that gene expression of key stress-related molecules plays an important role in determining the way an individual reacts to the environment and in the long-term consequences of cocaine exposure, thereby contributing to addiction liability.

5.2. Dopamine

Similar to outbred animals (Hooks et al., 1992; Marinelli and White, 2000), our data suggests that bHRs are "hyper-dopaminergic" relative to bLRs. Using fast scan cyclic voltammetry, we have shown that bHRs exhibit a greater number of spontaneous dopamine release events in the core of the nucleus accumbens (Flagel et al., 2010b). These findings seem to be in agreement with those in outbred animals demonstrating higher basal firing rates and bursting activity of DA neurons in the ventral tegmental area in HR rats (Marinelli and White, 2000). We have also shown that bHRs are more sensitive to the psychomotor-activating effects dopaminergic drugs (Flagel et al., 2010b). The underlying neurobiological mechanisms mediating these behavioral effects are unclear, but we do know that bHRs and bLRs differ in dopamine receptor expression. Similar to findings in outbred rats (Hooks et al., 1994), we have shown that bHRs have lower levels of dopamine D2 receptor mRNA expression in the dorsal striatum (Flagel et al., 2010b). However, we also found that bHRs have a higher proportion of $D2^{high}$ receptors, while the two phenotypes do not differ in total D2 binding capacity (Flagel et al., 2010b). We speculate that the increased proportion of $D2^{high}$ receptors in bHRs may account for the behavioral hypersensitivity in response to treatment with dopaminergic drugs, such as quinpirole, a D2/D3 agonist (Flagel et al., 2010b). In agreement, many treatments that result in functional supersensitivity to dopamine (e.g. amphetamine sensitization, cocaine self-administration) elicit a large increase in the proportion of $D2^{high}$ receptors in the striatum, even if they produce no change in the total number of receptors (Seeman et al., 2005, 2007; Briand et al., 2008). These findings may seem incongruent with imaging studies reporting lower levels of striatal D2 receptors in human cocaine addicts (Volkow et al., 1993; Martinez et al., 2004) and in animal models of addiction (Nader et al., 2006; Dalley et al., 2007); however, in each of these studies, the ligands used could not discriminate between the low- and high-affinity D2 receptor states. Given our findings in the bred animals, we speculate that a greater proportion of $D2^{high}$ receptors might be a neurobiological hallmark of addiction-prone individuals, rendering them hypersensitive to dopaminergic drugs, including cocaine.

5.3. Fibroblast growth factor family

Our interest in the fibroblast growth factor (FGF) family emerged from a study examining alterations in genome-wide expression profiles in the brains of patients suffering from major depressive disorder (MDD) (Evans et al., 2004). Using a "discovery" approach we found that members of the FGF family were significantly altered in MDD subjects, which led to a series of studies in animal models that have greatly advanced our understanding of the role of the FGF family in brain function and dysfunction (for review see Turner et al., 2012). Here we will focus on the role of FGF2 as an antecedent to drug-taking behavior and potential mediator of drug-induced neural plasticity.

The notion that FGF2 played a role in substance abuse was first put forth by Jane Stewart and colleagues. Studies from this group demonstrated that FGF2 levels are increased in the ventral tegmental area following repeated amphetamine treatment (Flores et al., 1998) and that endogenous FGF2 in the VTA is required for the induction of amphetamine sensitization (Flores et al., 2000) and drug-induced neural plasticity (Mueller et al., 2006). These findings have since been expanded to other drugs of abuse and other brain regions. Of particular interest is the work of Fumagalli and colleagues, showing enduring elevations of FGF2 in the mesocorticolimbic dopamine system following chronic cocaine exposure (Fumagalli et al., 2006), and highlighting interactions between FGF2 and dopamine D2 receptor in the prefrontal cortex and hippocampus (Fumagalli et al., 2003). These findings, together with the fact that bHRs and bLRs differ in basal FGF2 expression, led us to a series of studies in the bred lines investigating the role of this molecule in the initial response to drugs of abuse and in long-term neuroadaptations.

Relative to bLRs, bHRs have higher basal levels of FGF2 expression in the hippocampus and nucleus accumbens (Perez et al., 2009; Clinton et al., 2012). Further, we have recently uncovered basal epigenetic differences in the association of modified histones with FGF2 that are in agreement with the increased levels of mRNA in bHRs relative to bLRs (Chaudhury et al., unpublished data). We

also know that there is a differential effect of cocaine on the FGF system in the two phenotypes. Following either a one-week (Turner et al., 2008) or two-week (Waselus et al., 2013) sensitizing regimen of cocaine, we see changes in the FGF system in a phenotype-, brain-region- and time-dependent manner. Perhaps most striking are the cocaine-induced changes we see in FGF2 mRNA after 60 days of abstinence when compared to 1 day of abstinence. Interestingly, for bLRs, there is a decrease in FGF2 expression in the dentate gyrus of the hippocampus following prolonged abstinence, whereas for bHRs there is an increase in FGF2 mRNA in the core of the nucleus accumbens (Waselus et al., 2013). Thus, cocaine-induced changes in FGF2 expression following abstinence seem to be specific to the "stress circuitry" in bLRs and the "reward circuitry" in bHRs. These findings support the notion that the FGF system plays a role in mediating long-term drug-induced neuroadaptations, and may do so differently, perhaps by affecting different "circuits", in addiction-prone individuals.

While this body of work demonstrates that the FGF system is altered as a consequence of drug exposure, additional studies of ours provided evidence for a role of FGF in addiction liability prior to drug exposure. In particular, the role of the FGF family as an antecedent of drug-seeking behavior comes from studies examining the long-term effects of early life FGF treatment. Remarkably, we have shown in outbred animals that a single injection of FGF2 on the first day of life increases the acquisition of cocaine self-administration in adulthood (Turner et al., 2009). In the bred lines, we recently found that a single injection of FGF2 early in life affects bLRs to a greater extent than bHRs. Thus, in bLRs, which have lower basal levels of FGF2, high anxiety, and low propensity for drug-taking and drug-seeking behavior, FGF2 administration on the first day of life renders them more HR-like. As adults, FGF2-treated bLRs are less anxious (Turner et al., 2011), and more responsive to a sensitizing regimen of cocaine (Clinton et al., 2012). Further, neonatal FGF2 selectively increases D1 receptor and FGF2 mRNA in the core of the nucleus accumbens of bLRs, which likely contributes to their heightened cocaine sensitization (Clinton et al., 2012). Taken together, these studies demonstrate that FGF2 generally favors the "externalizing disorder" phenotype and represents a neuromolecular antecedent of vulnerability for substance abuse.

6. A role for the hippocampus in addiction liability

The hippocampus is best known for its role in learning and memory, and is becoming increasingly recognized for its role in processing emotionally salient information and in controlling behavior (e.g. Raber et al., 2011; Sahay et al., 2011; Zweynert et al., 2011; Kheirbek et al., 2012). Thus, it is not surprising that the hippocampus is repeatedly recognized as a locus of differences in gene expression and neural plasticity in the bred lines. We have uncovered dramatic differences in global gene expression profiles between bHRs and bLRs on postnatal days 7 and 14, and these findings were specific to the hippocampus, as gene expression differences in the core of the nucleus accumbens were relatively minimal (Clinton et al., 2011). Early in development the most profound gene expression differences in the hippocampus were related to neurodevelopmental processes and synaptogenesis, and these findings were accompanied by increased hippocampal volume and cell proliferation in bLRs relative to bHRs (Clinton et al., 2011). Interestingly, many studies in adult outbred HR/LR rats also report gene expression differences in the hippocampus (Rosario and Abercrombie, 1999; Kabbaj et al., 2000; Ballaz et al., 2008) as well as structural changes (Isgor et al., 2004) that are consistent with our findings in the developing bred animals.

Recent studies have identified a role for adult hippocampal neurogenesis in drug-taking behavior and relapse (Noonan et al., 2008, 2010). Interestingly, in adult bred animals, we have detected basal differences in the turnover of adult-born cells in the hippocampus, with bLRs showing similar birth rates, but lower rates of survival compared to bHRs (Perez et al., 2009). Not surprisingly, there are also phenotypic differences in hippocampal neurogenesis in response to cocaine. Exposure to a 1-week sensitizing regimen of cocaine results in decreased cell proliferation in bLRs, and these effects become amplified over the course of abstinence (Garcia-Fuster et al., 2010). In contrast, abstinence from cocaine decreased survival of mature neurons in bHRs (Garcia-Fuster et al., 2010), an effect that paralleled enhanced psychomotor sensitization in these animals. These findings support an association between impaired hippocampal function and greater behavioral sensitization to cocaine (Chambers and Taylor, 2004). While the exact role of new neurons in adult hippocampal function is unknown, one could speculate that the decrease in cell survival in bHRs during abstinence results in fewer functional connections between the hippocampus and reward-related limbic regions. Thus, impaired neurogenesis during abstinence may lead to maladaptive drug-seeking behaviors and relapse, feeding the vicious cycle of addiction.

In the bred lines, we have identified global differences in hippocampal gene expression during development, differences in expression of specific molecules in the hippocampus, including FGF2 and GR mRNA, and differences in adult neurogenesis under basal conditions and following cocaine exposure. Taken together, these findings suggest a major role of the hippocampus in mediating differences in temperament, environmental reactivity to stress, and overall vulnerability to addiction.

7. Summary and conclusions

Building on observations in both human studies and outbred animal models, we have generated a genetic rat model that underscores the importance of differences in vulnerability to drug-seeking behavior and the conversion to addiction. We have shown that this vulnerability is genetically based and is closely associated with a constellation of behavioral traits that mirror "temperament" in humans. Thus, our bHR animals have many characteristics of humans who are particularly vulnerable to externalizing disorders, whereas our bLR animals have characteristics of humans prone to internalizing disorders. We have noted that the behavioral disinhibition characteristic of the bHRs leads to a greater propensity to explore, act "impulsively", seek rewarding stimuli, associate these rewards with "signs" or cues, convert to addiction, and relapse. The bLRs generally have opposing characteristics, although they are not immune to drug abuse. Indeed, sufficient exposure to the drug can lead to similar levels of drug-taking behavior. Moreover, exposure to psychosocial stress can accelerate this process, thereby suggesting that both population extremes are vulnerable to drug-seeking, albeit as a result of different motives, and via different paths.

One of the greatest values of the selectively bred lines is that one can explore the question of antecedents of drug abuse. Addiction, like other complex disorders, is the product of gene by environment interactions, and the drug itself can be seen as one of the major environmental factors. But to prevent addiction, it is critical to understand the variables that precede exposure to the drug, that propel an individual to seek drugs and/or render that individual particularly vulnerable to addiction and relapse. These variables are likely a mix of complex genetic determinants, early life events, as well as more recent environmental triggers that lead to experimentation with drugs. Our model allows us to parse these variables

and show that, in fact, they are understandable at the molecular and genetic level and can be exacerbated or dampened prior to drug exposure. A case in point is the role of FGF2 in drug seeking behavior, where it appears to be a predisposing factor for decreased anxiety but greater exploration, and where modification of FGF2 early in life can alter sensitization to cocaine and self-administration behavior in adulthood. In fact, we have shown that FGF, GR, dopaminergic molecules and other neurotransmitters and neuromodulators (e.g. FADD, Garcia-Fuster et al., 2009) can play a role both in the initial addiction vulnerability as well as in the altered neural response following chronic drug exposure (Fig. 3). Thus, the selectively bred rat lines provide a means to identify molecular targets for preventive interventions and to uncover novel targets that might have otherwise gone unrecognized in outbred populations.

In sum, we have created selectively bred rat lines that differ on a number of neurobehavioral dimensions of relevance to addiction. Unlike outbred animals classified as high- and low-responders, bHRs and bLRs exhibit differences on a constellation of traits associated with addiction liability, including aggression, impulsivity and sign- and goal-tracking behaviors. We can therefore exploit this unique genetic animal model to identify neurobiological antecedents and consequences of drug abuse. Moreover, with the use of modern genomic tools, we are working to uncover genes implicated in bHR/bLR differences and new discoveries should provide additional targets for the treatment of addiction. Given that drugs of abuse have differing consequences on individuals as a function of their genetic endowments, this animal model could lead to the discovery of biomarkers that could guide more personalized treatment of substance abuse. Indeed, the discoveries from this body of work and other genetic animal models should provide new molecular candidates and treatment strategies for humans suffering from addictive disorders.

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