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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).