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Review

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.

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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 long-standing 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 ($n \geq 12$) 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).