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Individual differences in novelty-seeking behavior in spontaneously hypertensive rats: Enhanced sensitivity to the reinforcing effect of methylphenidate in the high novelty-preferring subpopulation

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HIGHLIGHTS

- Novelty seeking may predict vulnerability to drug abuse in ADHD individuals.
- SHRs showed inter-individual variations in novelty-seeking behavior.
- High novelty-preferring SHRs self-administered more methylphenidate.
- High novelty-seeking ADHD individuals may be at risk to misuse methylphenidate.

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ABSTRACT

Background: High novelty seeking has been assumed to predict vulnerability to use addictive drugs. Notably, it is also a symptom associated with attention-deficit/hyperactivity disorder (ADHD). The aim of this study was to identify whether spontaneously hypertensive rats (SHRs), putative animal models of ADHD, display individual differences in novelty-seeking behavior, and whether high novelty-seeking SHRs show enhanced sensitivity to the reinforcing effect of methylphenidate, the most commonly prescribed stimulant ADHD medication.
Methods: First, we established that SHRs show higher levels of novelty-seeking behavior than their normotensive control strain, Wistar Kyoto (WKY) rats. Novelty seeking was measured in two tests: open field test in a novel test arena, and novel object preference tests. Thereafter, SHRs were classified into high responders (HR) or low responders (LR), high novelty-preferring (HNP) or low novelty-preferring (LNP) rats, based on individual scores in the two behavioral assays. Methylphenidate self-administration was assessed thereafter.
Results: SHRs showed higher levels of novelty-seeking behavior than WKY rats. HR/LR and HNP/LNP subgroups were identified. HR and LR rats showed comparable rates of methylphenidate self-administration. However, HNP SHRs worked more for methylphenidate infusions than their LNP counterparts.
Conclusions: We showed some evidence on inter-individual variations in novelty seeking in SHRs. Importantly, we demonstrated enhanced sensitivity of HNP SHRs to the reinforcing effect of methylphenidate, indicating a "drug-vulnerable" SHR subpopulation. These findings are important as they may provide basis for a potential screening tool to identify a subset of ADHD patients (i.e. high novelty seekers) who may be at risk for misusing/abusing methylphenidate.

1. Introduction

Epidemiological studies have found significant associations between several distinct behavioral or personality traits, especially

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novelty-seeking behavior and impulsivity (Belin et al., 2008; Ebstein et al., 1996), and drug addiction (for review see Dawe and Loxton, 2004; Wills et al., 1994). Loosely defined, novelty-seeking is the individual tendency to explore and experience excitement in response to a novel stimulus (Cloninger, 1985), while impulsivity reflects poor control, carelessness and responding quickly with less precaution (Moeller et al., 2001). Furthermore, there have been some propositions that high impulsivity and novelty-seeking behavior may determine vulnerability to shift from controlled to compulsive drug use, i.e. drug addiction (Belin et al., 2008, 2011; Everitt et al., 2008; Perry and Carroll, 2008; Piazza et al., 1989, 1990).

Notably, novelty-seeking and impulsivity are also behavioral symptoms associated with the most common neurodevelopmental disorder of childhood, attention-deficit/hyperactivity disorder (ADHD) (Anckarsäter et al., 2006; Purper-Ouakil et al., 2010). Therefore, it is quite reasonable to suggest that the presence of these traits in ADHD individuals may increase their propensity to take drugs of abuse. Preclinical studies showed that animals which display ADHD-like phenotypes exhibited higher sensitivity to psychostimulants, opioids, cannabinoids, and other addictive drugs than their "normal" counterparts (for review see Vendruscolo et al., 2009), consistent with the observation on higher risk of ADHD subjects for substance abuse or addiction (Lee et al., 2011; Wilens and Morrison, 2011). Of note, some clinical studies reported moderate, if not, lack of significant associations between ADHD and incidence of drug abuse or drug dependence (Bernardi et al., 2012; Biederman et al., 1997, 2008). While differing outcomes can be explained by methodological differences employed across studies, it is also possible that findings from these studies were complicated by the heterogeneous nature of ADHD and also heterogeneity of ADHD subjects (Biederman and Faraone, 2001; Nigg et al., 2005; Purper-Ouakil et al., 2011).

Our group has been assessing the abuse and dependence liability of ADHD pharmacotherapies (e.g. methylphenidate, amphetamine and atomoxetine) in animal models of ADHD (dela Peña et al., 2010, 2011a,b, 2012, 2013a,b). In particular, we have been characterizing the abuse potential of methylphenidate, a stimulant drug which shows neurochemical and behavioral effects similar to cocaine, and is considered as the most commonly prescribed medication for ADHD (Heal et al., 2009). A previous study showed that methylphenidate is a "reinforcer" in that some ADHD patients chose the drug over placebo (Fredericks and Kollins, 2005; Kollins et al., 2009). Moreover, cases of ADHD patients abusing their stimulant medications have also been described (Jaffe, 1991; Poulin, 2007; Wilens et al., 2006, 2008).

While individual differences in pharmacological response to the drug may determine whether or not a person can be addicted to methylphenidate, it is also possible that personality or trait differences among ADHD subjects can influence enhanced propensity for methylphenidate misuse or abuse. Interestingly, a recent study reported differences in impulse control in adult ADHD patients with and without cocaine dependence and found that cocaine dependence was common among ADHD patients who showed higher levels of impulsivity (Crunelle et al., 2013). In line with the above, we hypothesized that ADHD individuals who show higher levels of impulsivity or novelty-seeking behavior will also display higher vulnerability to drug abuse. If this hypothesis is validated, it would follow that identifying the high novelty-seeking or impulsive ADHD subpopulation will enable us to determine ADHD patients at risk for future methylphenidate abuse or addiction. In turn, this will help in the development of screening methods to identify ADHD patients vulnerable for methylphenidate addiction, and eventually, provide an important factor for consideration when prescribing stimulant interventions for drug-vulnerable ADHD patients. The use of animal models may enable us to test this possibility directly.

The objective of this study is to identify whether spontaneously hypertensive rats (SHR), the most commonly used and validated animal model of ADHD (Russell et al., 2005; Sagvolden, 2000; Sagvolden et al., 2005), display individual differences in novelty-seeking behavior, and whether high (vs. low) novelty-seeking SHRs show higher sensitivity to the reinforcing effect methylphenidate. If proven true, this will lead to the identification of a "drug-vulnerable" SHR subpopulation at risk for methylphenidate addiction (Piazza et al., 2000). Individual differences in novelty seeking can be more accurately measured using various types of behavioral procedures. Moreover, the novelty-seeking trait has been identified in rats on the basis of either novelty-induced locomotor activity or preference for novel objects or a novel space (Belin et al., 2011; Cain et al., 2005; Klebaur et al., 2001). In line with the above, response to novelty was measured in two standard novelty-seeking tests: open field tests to gauge locomotor reactivity in a novel test arena (categorized as "forced" novelty-seeking test) (Belin et al., 2011; Dulawa et al., 1999; Thiel et al., 1999), and novel object preference ("free-choice" novelty) tests, described in previous studies (Bienkowski et al., 2001; Cain et al., 2005; Matthews et al., 2010).

2. Materials and methods

2.1. Animals

Male SHRs (10 weeks old, $n = 16$) were purchased from Orient Co. Ltd., a branch of Charles River Laboratories (Seoul, Korea) and housed in an environmentally-controlled animal room (temperature [$22 \pm 2\,^{\circ}C$] and humidity [$55 \pm 5\%$]). They were housed in groups (and individually thereafter during self-administration tests), and given access to food and water (except during behavioral assays) and maintained on a 12:12-h light/dark cycle. All tests were conducted during the light phase of the light/dark cycle. Behavioral assays commenced after one week of acclimatization. For preliminary studies, we determined differences in novelty-seeking behaviors between SHRs and their normotensive Wistar Kyoto (WKY) rat control strain. Thus, a separate cohort of SHRs ($n = 8$) and WKY ($n = 8$) were also subjected to open field and novel object preference tests (see below). All experiments were performed in accordance with the Principles of Laboratory Animal Care (NIH) and the Animal Care and Use Guidelines of Sahmyook University, Korea. Experiments were conducted in male rats only based on earlier clinical findings that stimulant therapy only influences the development of substance misuse in males, but not female subjects (Katusic et al., 2005).

2.2. Open field test: locomotor reactivity to novelty

Rats were placed individually in the center of an activity box (measuring 47 cm × 47 cm) bordered by 42 cm high side walls. Spontaneous activity of each rat was measured for 20 min using automated systems (Ethovision system, Noldus I.T. b.v., Netherlands). The distance traveled in the center of the arena, relative to the total distance moved in the open field was calculated for each rat, and values were used as an index of locomotor reactivity to novelty (Pogorelov et al., 2005).

2.3. Novel object preference test

The following day, rats were assessed for free-choice novel object preference. Experiments lasted for 3 days and divided into three phases: habituation, familiarization, and novel object preference. During habituation phase, rats were allowed to explore the empty box for 10 min. The following day, two identical objects (blue bottles) were placed in the testing area and then the rat was allowed