Journal of Affective Disorders 155 (2014) 247–254

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Dopamine depletion attenuates some behavioral abnormalities in a hyperdopaminergic mouse model of bipolar disorder

Jordy van Enkhuizen [a,b], Mark A. Geyer [a,c], Adam L. Halberstadt [a], Xiaoxi Zhuang [d], Jared W. Young [a,c,*]

[a] Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804, United States
[b] Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands
[c] Research Service, VA San Diego Healthcare System, San Diego, CA, United States
[d] Department of Neurobiology, University of Chicago, Chicago, IL, United States

ARTICLE INFO

Article history:
Received 26 June 2013
Accepted 12 August 2013
Available online 16 November 2013

Keywords:
AMPT
Bipolar disorder
Mice
Mania
Dopamine transporter

ABSTRACT

Background: Patients with BD suffer from multifaceted symptoms, including hyperactive and psychomotor agitated behaviors. Previously, we quantified hyperactivity, increased exploration, and straighter movements of patients with BD mania in the human Behavioral Pattern Monitor (BPM). A similar BPM profile is observed in mice that are hyperdopaminergic due to reduced dopamine transporter (DAT) functioning. We hypothesized that dopamine depletion through alpha-methyl-*p*-tyrosine (AMPT) administration would attenuate this mania-like profile.

Methods: Male and female DAT wild-type (WT; $n=26$) and knockdown (KD; $n=28$) mice on a C57BL/6 background were repeatedly tested in the BPM to assess profile robustness and stability. The optimal AMPT dose was identified by treating male C57BL/6 mice ($n=39$) with vehicle or AMPT (10, 30, or 100 mg/kg) at 24, 20, and 4 h prior to testing in the BPM. Then, male and female DAT WT ($n=40$) and KD ($n=37$) mice were tested in the BPM after vehicle or AMPT (30 mg/kg) treatment.

Results: Compared to WT littermates, KD mice exhibited increased activity, exploration, straighter movement, and disorganized behavior. AMPT-treatment reduced hyperactivity and increased path organization, but potentiated specific exploration in KD mice without affecting WT mice.

Limitations: AMPT is not specific to dopamine and also depletes norepinephrine.

Conclusions: KD mice exhibit abnormal exploration in the BPM similar to patients with BD mania. AMPT-induced dopamine depletion attenuated some, but potentiated other, aspects of this mania-like profile in mice. Future studies should extend these findings into other aspects of mania to determine the suitability of AMPT as a treatment for BD mania.

1. Introduction

Dysregulated dopamine neurotransmission is thought to contribute to several psychiatric disorders including bipolar disorder (BD) (Manji et al., 2003; Vawter et al., 2000). Polymorphisms in the dopamine transporter (DAT) gene have been associated with BD (Greenwood et al., 2006; Pinsonneault et al., 2011). These polymorphisms likely result in reduced cell surface expression and hence function of the DAT in patients (Horschitz et al., 2005). Indeed, reduced striatal levels of DAT have been observed in unmedicated patients with BD by using positron emission tomography (Anand et al., 2011) as well as in postmortem tissue (Rao et al., 2012). Hyperdopaminergia caused by reduced DAT function may therefore underlie many of the behavioral abnormalities observed in patients with BD.

Previously, we reported that patients with BD mania are hyperactive, exhibit increased object interactions, and walk in straight paths as quantified by the human Behavioral Pattern Monitor (BPM) (Minassian et al., 2011; Perry et al., 2009). This increased motor and exploratory activity is a cardinal feature of a manic episode and is described in the DSM-IV as an "increase in goal-directed activity" or "psychomotor agitation" (APA, 1994; Perry et al., 2010). Using a cross-species translational approach, we observed consistent behavioral patterns of mice with reduced functional DATs via either pharmacological or genetic manipulations (Perry et al., 2009; Ralph-Williams et al., 2003; Young et al., 2010a, 2010b). Specifically, mice treated acutely with the DAT inhibitor GBR12909 or constitutive DAT knockdown (KD) mice exhibit hyperactivity, increased specific exploration, and straighter paths of movement compared to controls in the mouse BPM. The hyperactivity of each model was attenuated after chronic treatment with the mood-stabilizer valproate (van Enkhuizen et al., 2013a). Moreover, we observed that the mania-like behavior of these mice is not limited to altered motor and exploratory activity

* Corresponding author. Tel.: +1 619 543 3582; fax: +1 619 735 9205.
E-mail address: jaredyoung@ucsd.edu (J.W. Young).

0165-0327/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2013.08.041

since these animals also exhibited increased risk preference in a gambling task (van Enkhuizen et al., 2013b; Young et al., 2011b).

Hence, DAT KD mice have proven to be a useful model for BD mania. The original DAT KD mice were on a mixed 129/S background however, and their phenotype was less stable than that produced by acute administration of GBR12909 to C57BL/6 mice (Young et al., 2010b). Despite the fact that one technique used pharmacological and the other genetic manipulations, we hypothesized that the discrepancy in stability was likely as a result of background strain (Young et al., 2010b). Indeed, the 129/S line of DAT wild-type (WT) and KD mice exhibited lower levels of activity than C57BL/6 mice as expected from these lines (Paulus et al., 1999). To better compare stability of the genetic model to that presented in the C57BL/6 pharmacological model, we have assessed the phenotypic stability of DAT KD mice on a C57BL/6 background.

Better models for BD are required in order to develop treatments targeted at the underlying mechanisms, as opposed to the serendipitous discovery of treatments as has occurred until now. For instance, aberrant motor and exploratory behavior are still observed in patients with BD, despite being on medication for 3 weeks (Minassian et al., 2011). Moreover, euthymic BD patients also still exhibit a hyperexploratory profile (Henry et al., 2013), poor risk learning (Adida et al., 2011), and poor cognitive function, particularly memory difficulties and impaired executive function (Martinez-Aran et al., 2004a, 2004b) compared with healthy subjects. Given the reduced DAT levels and hyperdopaminergic state of people with BD, reducing dopamine availability may theoretically normalize their neurochemical state and perhaps their behavior. Dopamine depletion can be induced by administration of alpha-methyl-*p*-tyrosine (AMPT). AMPT is a competitive inhibitor of tyrosine hydroxylase, the rate limiting enzyme in the synthesis of catecholamines from tyrosine (Booij et al., 2003; Engelman et al., 1968). Supporting this idea, pretreatment with AMPT blocked chlordiazepoxide/(+)-amphetamine-induced hyperactivity in mice without affecting activity of control mice (Davies et al., 1974). Moreover, AMPT treatment can reduce symptoms in patients with BD mania, while an increase in depression was observed in depressed patients treated with AMPT (Bunney et al., 1971). More recently, dopamine depletion with AMPT did not affect mood in patients with BD during treatment, but patients experienced a relapse of hypomanic symptoms post-depletion (Anand et al., 1999).

To assess whether dopamine depletion could rescue some of the cross-species quantified behavioral deficits relevant to BD mania, we examined the effects of AMPT in the DAT KD mouse model for BD mania, which have approximately 10% expression of the DAT and exhibit increased extracellular dopamine compared to control mice (Zhuang et al., 2001). We hypothesized that: (1) DAT KD mice on a C57BL/6 background would exhibit a BD mania-like profile in the BPM consistent with DAT KD mice on a 129/S background; (2) repeated testing of these mice would demonstrate a robust and stable phenotypic profile; and (3) catecholamine depletion by AMPT treatment would attenuate this mania-like behavioral profile.

2. Methods

2.1. Animals

Male C57BL/6J mice ($n=39$), DAT KD (male, $n=37$; female, $n=28$), and DAT WT (male, $n=32$; female, $n=34$) littermate mice were used throughout the three studies. DAT heterozygous breeders backcrossed onto a C57BL/6 background for more than 10 generations were sent to our laboratory from the University of Chicago. Male and female DAT KD and WT mice were generated from heterozygous breeding pairs. All mice were group housed (four/cage) and maintained in a temperature-controlled vivarium (21 ± 1 °C) on a reversed day–night cycle (lights on at 7.00 PM, off at 7.00 AM). Mice were 3–6 months old at the time of testing, weighed between 20 and 40 g, and were tested during the dark phase between 8.00 AM and 5.00 PM. Mice had ad libitum access to water and food (Harlan, Madison, WI, USA). All procedures were approved by the UCSD Institutional Animal Care and Use Committee. The UCSD animal facility meets all federal and state requirements for animal care and was approved by the American Association for Accreditation of Laboratory Animal Care.

2.2. Drug treatment

Alpha-methyl-*p*-tyrosine methyl ester hydrochloride (AMPT) (Sigma-Aldrich, St Louis, MO, USA) was dissolved in saline (10 ml/kg). AMPT or saline was administered to mice in three equal i.p. injections 24, 20, and 4 h prior to testing (Davies et al., 1974). Previous studies have shown that mouse brain dopamine and norepinephrine levels are reduced ~30–40% 4 h after administration of 40–80 mg/kg (i.p.) AMPT (Dobrzanski and Doggett, 1976; Flexner and Goodman, 1975).

2.3. Mouse behavioral pattern monitor

Locomotor behavior and exploration were examined using eight mouse BPM chambers (BPM; San Diego Instruments, San Diego, CA) as described previously (Risbrough et al., 2006; Tanaka et al., 2012). Each Plexiglas arena consists of a $30.5 \times 61 \times 38$ cm area with three floor holes and eight wall holes (three along each long side and one in each of the short sides; 1.25 cm in diameter, 1.9 cm from the floor), each equipped with an infrared photobeam to detect holepoking. An outer box with an internal white house-light above the arena (350 lx in the center and 92 lx in the four corners) minimized external light and noise. Activity was obtained from a grid of 12×24 infrared photobeams 1 cm above the floor (2.5 cm apart; 24×12 *X–Y* array), recording the location of the mouse every 0.1 s, with its position defined across nine unequal regions (four corners, four walls, and center (Geyer et al., 1986)). Another set of 16 photobeams, placed 2.5 cm above the floor, was used to detect rearing behavior. Mice were placed in the bottom left-hand corner of the arena and the test session started immediately. The primary outcome measures were transitions across the defined regions and center entries (locomotor activity), holepoking and rearing (exploratory behavior), and entropy (*h*) and spatial d (locomotor patterns). Lower entropy reflects predictable, ordered sequences of activity, while higher entropy indicates a greater disorder of movement. Spatial d quantifies the geometric structure of the locomotor path, where a value of 1 reflects a straight path, and 2 highly circumscribed small-scale movements (Paulus and Geyer, 1991).

Experiment 1. Female ($n=11$) and male ($n=17$) DAT KD mice and their female ($n=12$) and male ($n=14$) WT littermates were tested in the BPM to assess their exploratory profile. Activity was measured in the BPM for 60 min during the first test (Experiment 1a), then one week later for 60 min (Experiment 1b), and finally 10 days later for 180 min (Experiment 1c).

Experiment 2. The effects of AMPT on the exploratory profile of male C57BL6/J mice were assessed in the BPM for 60 min. Mice received saline or 10, 30, or 100 mg/kg AMPT 24, 20, and 4 h prior to testing ($n=10$/group).

Experiment 3. The effects of 30 mg/kg AMPT were assessed on the exploratory behavior of female ($n=17$) and male ($n=20$) DAT KD mice and their female ($n=22$) and male ($n=18$) WT littermates in the BPM for 60 min. These mice were not BPM naïve and had been treated with the antipsychotic risperidone six weeks earlier. The mice