Brain Research xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Brain Research

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

Research report

Effects of amphetamine exposure during adolescence on behavior and prelimbic cortex neuron activity in adulthood

Luke K. Sherrill [a], Joshua M. Gulley [a,b,c,*]

[a] Department of Psychology, University of Illinois, Urbana-Champaign, United States
[b] Neuroscience Program, University of Illinois, Urbana-Champaign, United States
[c] Carl R. Woese Institute for Genomic Biology, University of Illinois, Urbana-Champaign, United States

ARTICLE INFO

Article history:
Received 22 January 2018
Received in revised form 14 May 2018
Accepted 19 May 2018
Available online xxxx

Keywords:
Adolescent
Development
D_1receptor
D_2receptor
Locomotor activity
Sensitization

ABSTRACT

Repeated exposure to psychostimulants during adolescence produces long-lasting changes in behavior that may be mediated by disrupted development of the mesocorticolimbic dopamine system. Here, we tested this hypothesis by assessing the effects of amphetamine (AMPH) and dopamine receptor-selective drugs on behavior and neuron activity in the prelimbic region of the medial prefrontal cortex (PFC). Adolescent male, Sprague-Dawley rats were given saline or 3 mg/kg AMPH between postnatal day (P) 27 and P45. In Experiment 1, locomotor behavior was assessed during adulthood following challenges with a dopamine D_1 (SKF 82958) or D_2 (quinpirole) receptor-selective agonist. In Experiment 2, pre-exposed rats were challenged during adulthood with AMPH and a D_1 (SKF 83566) or D_2 (eticlopride) receptor-selective antagonist. In Experiment 3, the activity of putative pyramidal cells in the prelimbic cortex was recorded as rats behaved in an open-field arena before and after challenge injections with AMPH and one of the antagonists. We found that compared to controls, adolescent pre-exposed rats were more sensitive to the stimulant effects of AMPH and the dopamine receptor agonists, as well as to the ability of the antagonists to reverse AMPH-induced stereotypy. Prelimbic neurons from AMPH pre-exposed rats were also more likely to respond to an AMPH challenge in adulthood, primarily by reducing their activity, and the antagonists reversed these effects. Our results suggest that exposure to AMPH during adolescence leads to enduring adaptations in the mesocorticolimbic dopamine system that likely mediate heightened response to the drug during adulthood.

1. Introduction

Individuals with a long history of AMPH* misuse often exhibit impairments in tasks assessing executive cognitive functions such as impulse control, attention, working memory, and decision-making (McKetin and Mattick, 1998; Ornstein et al., 2000; Monterosso et al., 2005; Woods et al., 2005; Casaletto et al., 2015). Notably, however, cognitive impairment is not an inevitable consequence of repeated AMPH exposure (Scott et al., 2007; Hart et al., 2012) and the development of drug-induced cognitive dysfunction may depend on a number of ancillary factors. One such potential factor is the initial age of drug exposure, with those beginning drug use during adolescence being most at risk (Vonmoos et al., 2013). This hypothesis is supported indirectly by data showing that brain regions known to be important for cognition, including those in the corticolimbic circuitry such as the PFC, amygdala, and hippocampus, are among the last to develop adult-like structure and function, and appear highly susceptible to environmental influences such as drug use (Paus et al., 2008; Gulley and Juraska, 2013). In addition, cross-sectional analyses have suggested that those with the longest duration of psychostimulant abuse, which are individuals who started drug use in early adolescence, are the most susceptible to deficits in decision making (Rogers et al., 1999) and have a greater likelihood of developing a substance use disorder (Wu and Schlenger, 2003; Lopez-Quintero et al., 2011; Gilder et al., 2014).

The mechanisms that underlie this enhanced vulnerability of adolescents to the adverse consequences of repeated AMPH exposure are uncertain, but a leading candidate is drug-induced changes in the normal development of the mesocorticolimbic dopamine system (Gulley and Juraska, 2013). Studies in rodents have demonstrated that during adolescent development, there are significant changes in the density of monoamine transporters

* Corresponding author at: Department of Psychology and Neuroscience Program, University of Illinois at Urbana-Champaign, 731 Psychology Bldg MC-716, 603 E Daniel St, Champaign, IL 61820, United States.
E-mail address: jgulley@illinois.edu (J.M. Gulley).

* AMPH – amphetamine; PFC – prefrontal cortex; VTA – ventral tegmental area; NAc – nucleus accumbens; P – postnatal day

https://doi.org/10.1016/j.brainres.2018.05.028
0006-8993/

and dopaminergic fibers (Kalsbeek et al., 1988; Benes et al., 2000; Moll et al., 2000; Willing et al., 2017). Dopamine neurons in the VTA, which project to multiple areas including the PFC and NAc, have been shown to be more active during the adolescent period compared to adulthood and this appears to be due to a relatively reduced GABAergic tone in the adolescent VTA (McCutcheon et al., 2012). This finding is not unequivocal, however, as a recent study reported no age-dependent differences in baseline firing rates of VTA dopamine neurons (Kim et al., 2016). This study also showed neurons recorded from adolescents were less responsive to reward anticipation and delivery compared to those recorded from adults. In terms of receptors for dopamine, there is an over-production and subsequent decline of dopamine D_1 and D_2 receptor expression in the PFC and NAc as rats age from pre-adolescence into young adulthood (Andersen et al., 2000; Tarazi and Baldessarini, 2000; Brenhouse et al., 2008). It has also been suggested that signaling via D_1–D_2 heteromers, particularly in the striatum and NAc, is also unique in adolescents compared to adults and this may contribute to enhanced vulnerability in adolescents to the effects of abused drugs (Perreault et al., 2014).

In the current study, we tested the hypothesis that repeated exposure to AMPH during periadolescence (P27-P45) leads to long-lasting changes in the function of D_1 and D_2 receptors in adulthood. In Experiment 1, we investigated if adult rats pre-exposed to AMPH in periadolescence were sensitized to the motor-activating effects of the D_1-selective agonist SKF 82958 or the D_2-selective agonist quinpirole compared to saline-treated controls. In a second experiment, we tested if the D_1-selective antagonist SKF 83566 or the D_2-selective antagonist eticlopride would differentially influence AMPH-induced stereotypy in periadolescent pre-exposed rats compared to controls. Lastly, in Experiment 3 we used *in vivo* electrophysiology in periadolescent pre-exposed rats and controls to investigate functional changes in putative pyramidal cells of the prelimbic region of the medial PFC. Previous studies have revealed an important role of the medial PFC in AMPH-induced motor activation and sensitization (Steketee, 2003; Hall et al., 2009; Gulley and Stanis, 2010; Mathews and McCormick, 2012; Aguilar-Rivera et al., 2015). Moreover, the activity of pyramidal output cells is tightly regulated by D_1 and D_2 receptors (Seamans and Yang, 2004) and we recently found that periadolescent AMPH exposure alters D_1 receptor-mediated inhibition in these cells *in vitro* (Kang et al., 2016a; Paul et al., 2016).

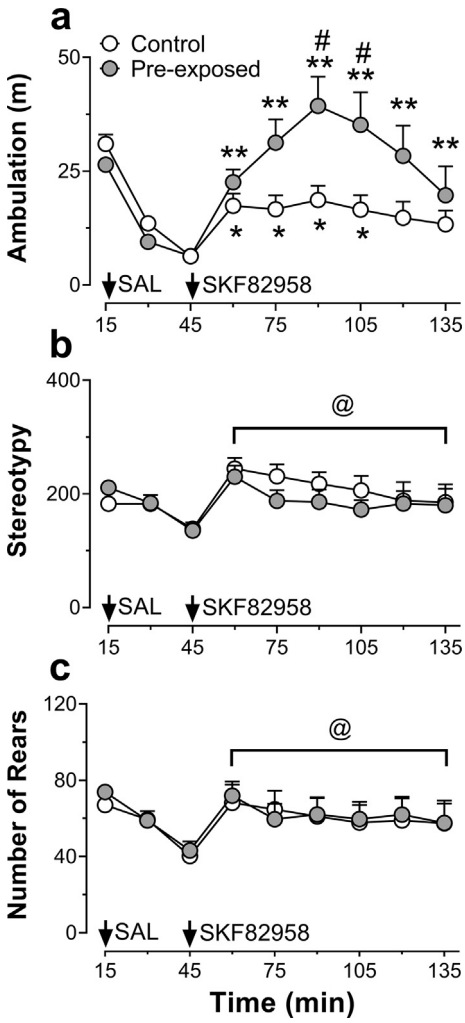

Fig. 1. Ambulation (a), stereotypy (b) and rearing (c) in an open-field arena following challenge with 1.0 mg/kg SKF 82958 (n = 11–12/group). Arrows indicate time-bins when rats were removed from the open-field and injected (i.p.) with saline and the D_1 agonist. $^{*}p < 0.05$, $^{**}p < 0.01$ vs baseline (45-min bin) within group; $^{\#}p < 0.05$ vs control within time bin; $^{@}p < 0.05$ vs baseline collapsed across group.

2. Results

2.1. Experiment 1 – Effects of AMPH pre-exposure on D_1 and D_2 agonist challenge

Relative to baseline, there was an increase in motor activity after injection with the D_1 agonist SKF 82958 in both controls and AMPH pre-exposed rats (Fig. 1). For ambulation, we found a significant main effect of time bin ($F_{8,168} = 16.7$, $p < 0.001$) and a significant group x time bin interaction ($F_{8,168} = 6.30$, $p < 0.001$). As shown in Fig. 1a, rats pre-exposed to AMPH had a significantly greater maximal response that persisted for the entire 90-min post-drug interval. The D_1 agonist also increased stereotypy (Fig. 1b) and rearing (Fig. 1c) behavior. Separate ANOVAs indicated significant main effects of time bin for stereotypy ($F_{8,168} = 5.79$, $p < 0.001$) and rearing ($F_{8,168} = 4.54$, $p < 0.001$). However, in contrast to ambulation, there were no significant main effects of group or group x time bin interactions (*ps* > 0.05).

During challenge sessions with the D_2 agonist quinpirole, rats pre-exposed to AMPH were more sensitive to drug-induced increases in ambulation (Fig. 2a). Two-way repeated measures ANOVA of these data revealed significant main effects of group ($F_{1,21} = 6.76$, $p < 0.05$) and time bin ($F_{8,168} = 97.5$, $p < 0.001$), as well as a significant group x time bin interaction ($F_{8,168} = 4.97$, $p < 0.001$). Pre-exposed rats showed a significant increase in agonist-induced ambulatory activity beginning 30 min post-injection, while the activity of control animals did not significantly change across the 90 min post-injection period. Similarly, analysis of stereotypy (Fig. 2b) indicated a significant main effect of time bin ($F_{8,168} = 22.3$, $p < 0.001$) and a significant group x time bin interaction ($F_{8,168} = 6.88$, $p < 0.001$). For rearing (Fig. 2c), there was a significant main effect of time bin ($F_{8,168} = 10.1$, $p < 0.001$) and a group x time bin interaction that was at the threshold for being considered statistically significant ($F_{8,168} = 1.20$, $p = 0.053$). Thus, for all three measures of motor activity, AMPH pre-exposed rats exhibited greater sensitivity to the effects of quinpirole.

2.2. Experiment 2 – Effects of AMPH pre-exposure on AMPH and D_1 or D_2 antagonist challenge

In a separate group of rats, we assessed the effects of AMPH pre-exposure on the response to a challenge injection of AMPH and to subsequent injection with a D_1 or D_2 antagonist. As shown in Fig. 3, a challenge injection of 3 mg/kg AMPH significantly increased