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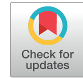
Prenatal stress leads to chromatin and synaptic remodeling and excessive alcohol intake comorbid with anxiety-like behaviors in adult offspring



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A B S T R A C T

Epidemiologic evidence suggests that individuals during their prenatal development may be especially vulnerable to the effects of environmental factors such as stress that predisposes them to psychiatric disorders including alcohol use disorder (AUD) later in life. Currently, the epigenetic mechanisms of anxiety comorbid with AUD induced by prenatal stress (PRS) remain to be elucidated. Here, we examined anxiety-like and alcohol drinking behaviors in adult offspring of prenatally stressed dam (PRS-mice) using elevated plus maze, light/dark box and two-bottle free-choice paradigm. It was found that PRS-mice exhibit heightened anxiety-like behaviors and increased alcohol intake in adulthood and these behavioral deficits were associated with a significant decrease in dendritic spine density (DSD) in medial prefrontal cortex (mPFC) relative to non-stressed mice (NS mice). To determine the mechanisms by which PRS reduces DSD, we examined the expressions of key genes associated with synaptic plasticity, including activity regulated cytoskeleton associated protein (*Arc*), spinophilin (*Spn*), postsynaptic density 95 (*Psd95*), tropomyosin receptor kinase B (*TrkB*), protein kinase B (*Akt*), mammalian target of rapamycin (*mTOR*) and period 2 (*Per2*) in mPFC of PRS and NS mice. The mRNA levels of these genes were significantly decreased in PRS mice. Methylated DNA and chromatin immunoprecipitation studies revealed hyper DNA methylation or reduced histone H3K14 acetylation on promoters of above genes suggesting that epigenetic dysregulation may be responsible for the deficits in their expression. Findings from this study suggest that prenatal stress induced abnormal epigenetic mechanisms and synaptic plasticity-related events may be associated with anxiety-like and alcohol drinking behaviors in adulthood.

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1. Introduction

The alcohol use disorder (AUD) is highly prevalent among people with mood disorders, including anxiety and depression and contribute a gross public health burden globally (Bijl and Ravelli, 2000; Burns and Teesson, 2002; Hasin et al., 2007). Recent studies show that people with anxiety/depressive disorders have an increased risk to develop alcohol use disorders (de Graaf et al., 2003; Robinson et al., 2009; Schuckit and Hesselbrock, 1994; McDonald and Meyer, 2011). Several studies have also demonstrated strong association with anxiety-like and alcohol drinking behaviors in preclinical models (Pandey et al., 2004, 2017). Also, adolescent intermittent alcohol exposure leads to development of anxiety-like and alcohol drinking behaviors in rats during adulthood (Kyzar et al., 2016, 2017). In addition, accumulated evidence suggests that molecular mechanisms of AUDs and anxiety behaviors may be associated with epigenetic dysregulation of candidate genes in specific neurocircuitry via chromatin remodeling characterized by aberrant DNA methylation and histone modifications that leads to altered gene expressions (Tsankova et al., 2007; Mehler, 2008; Day et al., 2015; Pandey et al., 2017; Starkman et al., 2012; Qiang et al., 2014; Warnault et al., 2013; Ponomarev, 2013; Manzardo et al., 2013; Barbier et al., 2015).

Epidemiologic evidence accumulated over decades suggests that individuals during their prenatal development may be

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especially vulnerable to the effects of environmental factors that predispose them to psychiatric disorders including alcoholism later in life (Becker et al., 2011; Gordon, 2002; Sinha, 2007, 2008; Uhart and Wand, 2009; Charil et al., 2010; Fine et al., 2014; Markham and Koenig, 2011; Mulder et al., 2002; Fumagalli et al., 2007; Weinstock, 2008). Currently, precise molecular mechanisms in the specific brain regions due to prenatal stress-induced epigenetic changes in the development of the comorbidity of anxiety and alcoholism remain unclear. We recently found that adult offspring (mice) born from prenatally stressed dams (referred as PRS-mice) exhibited anxiety-like behaviors characterized by reduced social interaction and it has been established that these behavioral changes may be attributed to altered DNA methylation profiles and disrupted chromatin structures in genes associated with mental disorders such as *Bdnf*, *Gad1 and Relin* in the medial frontal cortex (mPFC) (Dong et al., 2014, 2016; Zheng et al., 2016; Matrisciano et al., 2013). However, it is not clear whether long-lasting epigenetic reprogramming induced by prenatal stress leads to alteration of dendritic spine density and genes associated with synaptic plasticity since abnormal synaptic plasticity plays an important role in the pathogenesis of neuropsychiatric disorders including anxiety, depression and alcoholism (Segal, 2005; Fagiolini et al., 2009). In addition, since anxiety often predisposes one to increase of alcohol consumption, it is necessary to explore whether prenatal stress induced anxiety-like behaviors is comorbid with altered alcohol drinking behaviors. Therefore, in this study, we first examined the effects of prenatal stress on behavioral phenotypes of anxiety and alcohol consumption in adult offspring using PRS mouse model. We also investigated spine densities and epigenetic changes in the genes associated with spine formation and plasticity in the mPFC of PRS and control adult mice. We focused our study in mPFC, as this region has been shown to play a major role in vulnerability to stress and also is associated with neuropsychiatric disorders including AUD (Duman et al., 2016; Bludau et al., 2016; Heilig et al., 2017). Our novel results suggest that prenatal stress can lead to long-lasting epigenetic modifications of synaptic plasticity-associated genes, thereby causing synaptic remodeling in mPFC and producing behavioral phenotypes of anxiety and alcoholism in adult offspring.

2. Methods

2.1. Animals and PRS procedure

All procedures were performed according to NIH guidelines for animal research (Guide for the Care & Use of Laboratory Animals, NRC, 1996) and were approved by the Animal Care Committee of the University of Illinois at Chicago. Pregnant mice (Swiss albino ND4, Harlan, Indianapolis, IN, USA) were individually housed with a 12-h light–dark cycle, and food and water *ad libitum*. Control dams were left undisturbed throughout gestation, whereas stressed dams were subjected to repeated episodes of restraint stress, as described previously (Dong et al., 2014, 2016; Zheng et al., 2016; Matrisciano et al., 2013). The stress procedure consisted of restraining the pregnant dam in a transparent tube (12×3 cm) under a bright light for 45 min three times per day from the seventh day of pregnancy until delivery. After weaning (PND 21), prenatally stressed (PRS) and non-stressed (NS) male mice were selected for the study and housed five per cage separately by condition. A maximum of one or two male pups was taken from each litter for each measure to remove any litter effects (Becker and Kowall, 1977; Chapman and Stern, 1979). All behavioral tests, including drinking experiments were performed in one set of mice whereas biochemical measurements in the brain were conducted in separate sets of mice that were not subjected to behavioral tests.

2.2. Behavioral experiments

2.2.1. Elevated plus-maze test (EPM)

To examine the anxiety behavior of gestational-stress offspring, the elevated plus-maze was performed in similar way as described by us (Pandey et al., 2015). Briefly, it consisted of two open and two closed arms (all arms: $30 \text{ cm} \times 5 \text{ cm}$) and was made of Plexiglas. The open arms were surrounded by 4 mm-high edges. The closed arms had transparent 14.5 cm high Plexiglas walls at the sides and end. The floor was made of black Plexiglas and elevated to a height of 50 cm above the floor. At the start of each test, mice were placed individually on the central platform and their behavior monitored by computer for 10 min. The number of entries for each arm and the time spent in each arm were recorded and analyzed. The percentage of open arm entries (open arm entries $\times 100$/total arm entries) and percentage of time spent in open arm (time spent in open arm $\times 100$/time spent in open and closed arms) were used as indices of anxiety. The number of closed arm entries is represented as general activity of mice.

2.2.2. Light/dark box exploration test (LDB)

The LDB consists of a dark compartment without illumination and a light compartment with illumination (0.25 Amp; light-emitting diode light). Both compartments are connected through an opening. On the day of testing, each mouse was allowed a 5-min pretest habituation period in the room before testing. Then, the mouse was gently placed in the dark compartment with its head facing away from the opening. The mouse was observed for a 5-min test period, and the time spent in each compartment was monitored and recorded by computer. The percentage of time spent in either the dark compartment or light compartment was calculated for each animal. Total ambulation in the light and dark compartments was represented as the general activity of the mouse (Pandey et al., 2015; Sakharkar et al., 2014).

2.2.3. Alcohol preference

Alcohol preference was measured by the two-bottle free-choice paradigm (Pandey et al., 2004). Mice were placed in individual cages and have *ad libitum* access to food and water, in two bottles, and were habituated to drink water from either bottle. Bottle positions were changed daily so that the mice would not develop a position habit. Once they started drinking water equally from either bottle, mice were provided with 3% (v/v) alcohol solution in one bottle and water in the other bottle daily for 3 days, and then concentrations of ethanol were increased to 7% for 3 days, 9% for 3 days and to 12% for another 3 days. Consumption of ethanol and water (ml) was measured daily at 6:00 p.m., and fresh water and ethanol (3, 7, 9, or 12%) solution in water were provided every day at the start of dark cycle. The mean percentage of alcohol intake and the percentage of water intake were calculated from their total fluid intake for 3 days for 3, 7, 9, and 12% alcohol. We measured body weight of mice before and after each dose of alcohol. The alcohol intake was presented as g/kg/day.

2.3. Histological study

2.3.1. Spine density measurement

The Golgi-Cox staining procedure was performed to measure the dendritic spine density in the pyramidal neurons of mPFC using the FD Rapid Golgi Stain Kit (Pandey et al., 2008). Brains were rapidly immersed in impregnation solution for at least 2 week. Then 200 µm brain sections were cut, mounted and stained according to the protocol provided by Kit manufacturer. After staining, sections were dehydrated and cleared in xylene solution and then cover slipped using mounting medium. Sections were

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