BRAIN RESEARCH 1641 (2016) 291–305

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Brain Research

Review

Genetically determined differences in noradrenergic function: The spontaneously hypertensive rat model

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ARTICLE INFO

Article history:
Accepted 12 November 2015
Available online 23 November 2015

Keywords:
SHR
WKY
ADHD
Maternal separation
GABA
NMDA

ABSTRACT

While genetic predisposition is a major factor, it is not known how development of attention-deficit/hyperactivity disorder (ADHD) is modulated by early life stress. The spontaneously hypertensive rat (SHR) displays the behavioral characteristics of ADHD (poorly sustained attention, impulsivity, hyperactivity) and is the most widely studied genetic model of ADHD. We have previously shown that SHR have disturbances in the noradrenergic system and that the early life stress of maternal separation failed to produce anxiety-like behavior in SHR, contrary to control Sprague–Dawley and Wistar–Kyoto (WKY) who showed typical anxiety-like behavior in later life. In the present study we investigated the effect of maternal separation on approach behavior (response to a novel object in a familiar environment) in preadolescent SHR and WKY. We also investigated whether maternal separation altered $GABA_A$ and NMDA receptor-mediated regulation of norepinephrine release in preadolescent SHR and WKY hippocampus. We found that female SHR, similar to male SHR, exhibited greater exploratory activity than WKY. Maternal separation significantly increased $GABA_A$ receptor-mediated inhibition of glutamate-stimulated release of norepinephrine in male and female SHR hippocampus but had no significant effect in WKY. Maternal separation had opposite effects on NMDA receptor-mediated inhibition of norepinephrine release in SHR and WKY hippocampus, as it increased inhibition of both glutamate-stimulated and depolarization-evoked release in SHR hippocampus but not in WKY. The results of the present study show that noradrenergic function is similarly altered by the early life stress of maternal separation in male and female SHR, while GABA- and glutamate-regulation of norepinephrine release remained unaffected by maternal separation in the control, WKY, rat strain.

This article is part of a Special Issue entitled SI: Noradrenergic System.

Abbreviations: ^{3}[H]NE, radioactively labelled norepinephrine; LC-NE, locus-coeruleus norepinephrine; P, post-natal day; SHR, spontaneously hypertensive rat; WKY, Wistar–Kyoto rat.

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http://dx.doi.org/10.1016/j.brainres.2015.11.019
0006-8993/

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder characterised by behavioral symptoms which include impulsivity, hyperactivity, and poor performance in tasks that require sustained attention, behavioral inhibition and time reproduction (American Psychiatric Association, 2013; Arnsten, 2006; Faraone and Doyle, 2000; Kerns et al., 2001). ADHD has a strong genetic component; twin studies showed that heritability is approximately 76% (Faraone et al., 2005). A number of environmental factors contribute to the development of ADHD. These include prenatal stress (Rodriguez and Bohlin, 2005), exposure to alcohol, cocaine and/or nicotine (Linares et al., 2006; Linnet et al., 2003; Mick et al., 2002) and postnatal/childhood stress (Biederman et al., 1995; Roy et al., 2000). Although considerable evidence suggests that early life stress interacts with genetic predisposition to determine the ADHD phenotype, rodent studies investigating interactions between genetic predisposition and early life stress are limited.

The spontaneously hypertensive rat (SHR) exhibits the major symptoms of ADHD and is widely used as a genetic model of ADHD (Knardahl and Sagvolden, 1979; Sagvolden, 2000). Previous behavioral studies of SHR in our laboratory have shown the strain to present with high levels of locomotor activity and low levels of anxiety-like and depression-like behaviors compared to their Wistar–Kyoto (WKY) progenitor rat strain (Okamoto and Aoki, 1963) and Sprague–Dawley rats (Howells et al., 2009; Sterley et al., 2011; Womersley et al., 2011). Anxiety and depression often occur as comorbid conditions in children with ADHD (Steinberg and Drabick, 2015). SHR have the advantage in that they provide a model of the behavioral symptoms of ADHD independent of anxiety-and depression-like behaviors.

Neurochemical investigations in our laboratory have shown that noradrenergic function is disturbed in SHR. These findings are relevant since all drugs used in therapeutic treatment of ADHD influence norepinephrine transmission. Methylphenidate, amphetamine, and atomoxetine all increase synaptic levels of norepinephrine in various parts of the brain, including the prefrontal cortex and hippocampus, through blockade of the norepinephrine transporter (Berridge et al., 2006; Bymaster et al., 2002; Kuczenski and Segal, 2002, 1997; Robertson et al., 2009; Swanson et al., 2006). Guanfacine is also effective in treating behavioral symptoms of ADHD, and directly activates postsynaptic α_{2A}-adrenoceptors (Arnsten et al., 2007; Arnsten, 2010). Our research on SHR shows that autoreceptor-mediated inhibition of norepinephrine release is impaired and glutamate stimulation of norepinephrine release is greater than that of WKY and Sprague–Dawley rats, in prefrontal cortex and hippocampus (Howells and Russell, 2008; Howells et al., 2009; Russell et al., 2000; Russell and Wiggins, 2000).

A number of neurochemical differences between SHR and control rat strains are evident in the hippocampus (Howells and Russell, 2008; Sterley et al., 2013a, 2013b). The hippocampus is essential for the development of neural networks that encode cognitive/spatial/item-in-context/episodic memory, important for behavioral inhibition and time reproduction (Goodman et al., 2014). These hippocampal-dependent