Psychoneuroendocrinology 65 (2016) 109–117

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Adolescent chronic stress causes hypothalamo–pituitary–adrenocortical hypo-responsiveness and depression-like behavior in adult female rats

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ARTICLE INFO

Article history:
Received 29 July 2015
Received in revised form 8 December 2015
Accepted 10 December 2015

Keywords:
Adolescence
Chronic variable stress
Neuroendocrine
Depression
Female rodent

ABSTRACT

Adolescence is a period of substantial neuroplasticity in stress regulatory neurocircuits. Chronic stress exposure during this period leads to long-lasting changes in neuroendocrine function and emotional behaviors, suggesting adolescence may be a critical period for development of stress vulnerability. This study investigated the effects of exposure to 14 days of chronic variable stress (CVS) in late-adolescent (pnd 45–58) female rats on neuroendocrine function, neuropeptide mRNA expression and depressive-like behavior in adolescence (pnd 59) and in adulthood (pnd 101). Adult females exposed to CVS in adolescence have a blunted hypothalamo-pituitary-adrenocortical (HPA) axis in response to a novel stressor and increased immobility in the forced swim test. Blunted HPA axis responses were accompanied by reduced vasopressin mRNA expression in the paraventricular nucleus of the hypothalamus (PVN), suggesting decreased central drive. Adolescent females tested immediately after CVS did not exhibit differences in stress reactivity or immobility in the forced swim test, despite evidence for enhanced central HPA axis drive (increased CRH mRNA expression in PVN). Overall, our study demonstrates that exposure to chronic stress in adolescence is sufficient to induce lasting changes in neuroendocrine drive and behavior, potentially altering the developmental trajectory of stress circuits as female rats age into adulthood.

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1. Introduction

Onset of stress-related psychopathologies (e.g., depression) often occurs during late adolescence (Kessler et al., 2003; Lewinsohn et al., 1999) and is frequently precipitated by chronic stress (Ge et al., 2006; Goodyer et al., 1998; Ham and Larson, 1990; Larson et al., 1990; Rudolph and Hammen, 1999). Women are twice as likely as men to develop stress-related psychopathologies (Kessler et al., 1993; Kuehner, 2003) indicating that sex is an important determinant of disease susceptibility. Recent rodent studies indicate that exposure to chronic stress during adolescence results in greater and longer-lasting changes in behavior and hypothalamo-pituitary-adrenocortical (HPA) axis function in females than in males (Bourke and Neigh, 2011; McCormick et al., 2008). Taken together, these findings suggest that exposure to chronic stress during the period of adolescence can lead to changes in endocrine and brain function that may predispose individuals, females in particular, to the development of stress-related psychopathologies.

Adolescence is an important developmental time-point in brain development, and is a period of active neuroplasticity in important neural pathways involved in stress regulation and HPA axis function (Andersen and Teicher, 2008; Andersen, 2003; Eiland and Romeo, 2013). The period of adolescence in rats can be subdivided into early or pre-pubertal adolescence (pnd 27–34), mid or pubertal adolescence (pnd 34–46) and late or post-pubertal adolescence (pnd 47–59). These time periods are characterized by differential development of critical stress-regulatory regions including the hippocampus, prefrontal cortex (PFC) and the amygdala. Prior studies indicate exaggerated and prolonged HPA axis stress responses in (male and female) adolescents relative to adults (Romeo et al., 2004a,b), suggesting a connection between the relative immaturity of stress circuits and enhanced HPA axis drive. Moreover, male rats exposed to a chronic variable stress (CVS) paradigm during

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http://dx.doi.org/10.1016/j.psyneuen.2015.12.004
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late adolescence are particularly sensitive to the somatic and neuroendocrine effects of chronic stress compared to early-adolescent rats (Jankord et al., 2011), indicating that late adolescence, the period encompassing final maturation of PFC-amygdala connections (Andersen and Teicher, 2008; Andersen, 2003), may represent a time period of stress hypersensitivity. Together, these findings suggest a potential amplification of the impact of stress on neural targets during this period of life, which may have lasting consequences on stress reactivity (HPA axis function, behavior) later in life.

Despite knowledge that the adolescent period is vulnerable to the effects of stress, and that females seemed to be preferentially susceptible to stress-related diseases (Kessler et al., 1993), little is known about the mechanisms by which stress may alter the development of the female adolescent brain. The purpose of this study was to assess the long-term impact of adolescent exposure to chronic stress on stress reactivity and stress-related behaviors in female rats.

2. Materials and methods

2.1. Animals

Twelve timed-pregnant (E10) Sprague-Dawley rats were obtained from Harlan (Indianapolis, IN, USA). Pups were born approximately one week after the arrival of the pregnant dams and remained with their mothers until weaning at pnd 25 of age. Only female rats were used for this experiment. At weaning, littermates were separated by sex and housed two per cage. Rats were divided into four experimental groups: CVS adolescent (adolescent CVS exposure, tested in adolescence, $n = 12$), control adolescent ($n = 10$), CVS adult (adolescent CVS exposure, tested in adulthood, $n = 12$), control adult ($n = 10$). In order to avoid any littermate effects, each group contained at least 10 rats from different litters with no more than one pup from the same dam. CVS animals were exposed to chronic variable stress paradigm during adolescence (pnd 45–58). Rats in the adolescent group (CVS and control) were subsequently exposed to the forced swim stress (FST) on pnd 59 and killed 24 h after exposure. Rats in the adult group (CVS and control) were exposed to the FST on pnd 101 and killed 24 h after exposure (Fig. 1A). All animals had ad libidum access to food and water throughout the experiment. Rats were housed in standard rooms controlling for humidity, temperature and light (0600–1800 h). All animal procedures were performed as approved by the University of Cincinnati Institutional Animal Care and Use Committee.

2.2. Adolescent chronic variable stress (CVS)

All female rats in the CVS group underwent 14 days of our standard CVS paradigm during adolescence (pnd 45–58). The CVS paradigm contained a battery of unpredictable variable stressors as previously described (Jankord et al., 2011). In short, animals were exposed to a morning stressor (0800–1100 h) and an afternoon stressor (1300–1700) every day of the experiment. The stressors included (1) 1 h shaker stress (100 rpm), (2) 1 h cold room (4C), (3) 5 min open field, (4) 30 min hypoxia exposure (8% O2 and 92% N2) (5) 1 h restraint. In addition, animals were exposed (~every third night) to overnight stressors, including single house or social crowding (6 rats per standard cage). Swimming was not used as a CVS stressor to ensure that FST was a novel stressor. All animals were exposed to the same stress protocol, which exactly replicated the sequence used in our prior study in males (Jankord et al., 2011).

2.3. Forced swim test and HPA axis assessment

2.3.1. Forced swim test

All animals were exposed to the FST to investigate the HPA axis response to a novel stressor as well as to assess depression-like behavior. Female rats in the adolescent group (CVS and Control) were subjected to the FST the morning following the last day of CVS (pnd 59). Adult animals (CVS and Control) were exposed to the FST forty-three days after the last CVS stressor (pnd 101), and consequently any observed behavioral or physiological changes would be due to enduring effects of experiencing CVS during the adolescent period. In all cases, animals were placed in a cylindrical tank containing water to 30 cm height (23C) for 10 min. Video recordings were taken from the side to allow full body visualization and facilitate future behavioral analysis. As previously described, the videos were analyzed and scored by a separate observer blinded to the experimental groups (Wulsin et al., 2010). Briefly, we assessed time-spent immobile, swimming, climbing and diving. At the end of the test, rats were removed from the cylinders and returned to their home cage.

2.3.2. HPA axis assessment

Blood samples were collected via tail vein clip at 5 min, 15 min, 30 min, 60 min and 120 min after cessation of FST (i.e., 15 min after stress induction) (Vahl et al., 2005). Corticosterone (CORT) and adrenocorticotropin hormone (ACTH) levels were measured by radioimmunoassay as previously described (Ostrander et al., 2006; Solomon et al., 2014; Wulsin et al., 2010). CORT concentration was determined using ^{125}I RIA kits (MP Biomedicals Inc., Orangerburg NY). ACTH was determined by radioimmunoassay, using ^{125}I ACTH as trace (Amersham Biosciences) ACTH antiserum donated by Dr. William Engeland (University of Minnesota) at a 1:120,000 dilution (Ulrich-Lai et al., 2006). In order to minimize hormonal variability due to circadian fluctuations, all procedures were performed during circadian nadir (0800–1200) of the diurnal CORT rhythm. Basal CORT levels were taken the day of sacrifice (24 h post-CVS).

2.4. Tissue harvesting and mRNA in-situ hybridization

The morning following FST, rats were rapidly decapitated (Zhang et al., 2009). Brains were removed and fast-frozen by immersion in isopentane on dry ice (−45 °C) and stored at −80 °C. Thymus and adrenals were removed, cleaned and weighed for analysis. Brains were sectioned and mounted onto slides in a one-in 12 series. In situ hybridization assays were performed as previously described (Seroogy and Herman, 1997). Briefly, antisense cRNA probes complementary to glucocorticoid receptor (GR) (456 bp) (McCullers et al., 2002), corticotropin releasing hormone (CRH) (765 bp) (Figueiredo et al., 2003), oxytocin (OXT) (477 bp) (Jankord et al., 2011), and vasopressin (AVP) (161 bp) (Herman, 1995) were generated by in vitro transcription using ^{35}S UTP. Tissue sections from all groups were processed in a single assay for each probe. The regions of interest included the PVN (parvocellular PVN: pPVN, dorsal pPVN, lateral pPVN, ventral zone of the medial pPVN; magnocellular PVN mPVN: anterior mPVN), hippocampus (CA1, CA3 and dentate gyrus), supraoptic nucleus (SON), and central amygdaloid nucleus (Paxinos and Watson, 1998). Tissue sections from all groups were included in a single in situ hybridization run. Images from autoradiographs were taken using a digital camera under controlled illumination.

Scion Image 1.62 software (Scion, Frederick MD) was used to perform a semi-quantitative analysis of the density of mRNA expression. Details of the analysis have been previously published (Jankord et al., 2011). Briefly, the region of interest was outlined and Scion Image was used to calculate the gray level units within the area of interest. The corrected gray level (CGL) was obtained

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