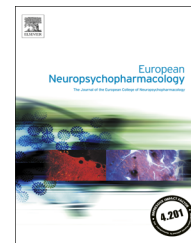




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Vulnerability versus resilience to prenatal stress in male and female rats; Implications from gene expression profiles in the hippocampus and frontal cortex

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Abstract

Adverse life events during pregnancy may impact upon the developing fetus, predisposing prenatally stressed offspring to the development of psychopathology. In the present study, we examined the effects of prenatal restraint stress (PS) on anxiety- and depression-related behavior in both male and female adult Sprague-Dawley rats. In addition, gene expression profiles within the hippocampus and frontal cortex (FC) were examined in order to gain more insight into the molecular mechanisms that mediate the behavioral effects of PS exposure. PS significantly increased anxiety-related behavior in male, but not female offspring. Likewise, depression-related behavior was increased in male PS rats only. Further, male PS offspring showed increased basal plasma corticosterone levels in adulthood, whereas both PS males and

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females had lower stress-induced corticosterone levels when compared to controls. Microarray-based profiling of the hippocampus and FC showed distinct sex-dependent changes in gene expression after PS. Biological processes and/or signal transduction cascades affected by PS included glutamatergic and GABAergic neurotransmission, mitogen-activated protein kinase (MAPK) signaling, neurotrophic factor signaling, phosphodiesterase (PDE)/ cyclic nucleotide signaling, glycogen synthase kinase 3 (GSK3) signaling, and insulin signaling. Further, the data indicated that epigenetic regulation is affected differentially in male and female PS offspring. These sex-specific alterations may, at least in part, explain the behavioral differences observed between both sexes, i.e. relative vulnerability versus resilience to PS in male versus female rats, respectively. These data reveal novel potential targets for antidepressant and mood stabilizing drug treatments including PDE inhibitors and histone deacetylase (HDAC) inhibitors. © 2012 Elsevier B.V. and ECNP. All rights reserved.

1. Introduction

Environmental adversity, either physical or emotional, experienced by the mother during pregnancy, may impact upon the developing fetus, adversely affecting its physical and mental wellbeing in later life. In humans, prenatal stress (PS) has been associated with the development of various cognitive and affective disorders, such as depression and anxiety (Huizink et al., 2004; Van den Bergh et al., 2005; Weinstock, 2001). Likewise, PS in rats has been associated with altered stress responsivity and increased anxiety- and depression-related behavior, see review by Huizink et al. (2004). These behavioral effects of PS can be counteracted by treating prenatally stressed rat offspring with various kinds of antidepressants (Alonso et al., 1999; Morley-Fletcher et al., 2003a, 2004; Poltyrev et al., 2005; Poltyrev and Weinstock, 2004). Therefore, PS in rats is regarded as a valid 'etiological' animal model to obtain more insight into the pathophysiology of affective disorders.

Similar to the human situation, the effects of PS exposure in rats are highly sex-dependent. More specifically, PS in Sprague-Dawley rats has been shown to particularly affect male offspring, whereas females are relatively resilient at the behavioral level (Zuena et al., 2008). Along similar lines, e.g. the hippocampus - a brain structure that is subject to sex-dependent development and is well-known for its role in affective regulation - has been shown to be differentially affected by PS in male and female rat offspring, which is indicative of sex-specific vulnerability to disturbed glutamatergic and GABAergic neurotransmission and reduced hippocampal neuroplasticity (e.g. Zuena et al., 2008; Morley-Fletcher et al., 2011; Laloux et al., 2012).

In the present study, we examined the effects of PS in both male and female Sprague-Dawley rats. Adult anxiety- and depression-related behavior was studied using the elevated zero maze test, the home cage emergence test, the forced swim test, and the sucrose intake test. Further, basal and stress-induced activity of the hypothalamus-pituitary-adrenal (HPA) axis was studied. Finally, we examined the effects of PS on gene expression profiles within the hippocampus and frontal cortex (FC), two brain regions known to be critically involved in the pathophysiology of depressive disorders and the response to antidepressant treatment (Sheline et al., 2003; Taylor et al., 2008). For this purpose, as a *hypothesis-generating* approach, a whole genome microarray-based design was used in order to

identify the genes and related molecular pathways that mediate vulnerability versus resilience to the behavioral effects of developmental stress exposure in male and female PS offspring, respectively.

2. Experimental procedures

2.1. Animals and procedures

This study was approved by the Animal Ethics Board of the Maastricht University, The Netherlands. Acclimatized Sprague-Dawley rats (Charles River, The Netherlands) were used. The animals were housed individually within a temperature-controlled environment (21 ± 1 °C) with a 12 h light/12 h dark cycle (lights on from 7.00-19.00 h) and had access to standard rat chow and water ad libitum. Pregnancy was determined by observation of vaginal plugs (embryonic day 0-E0). Restraint stress was performed daily during the last week of pregnancy (E14-E21). Pregnant female rats ($n=8$) were individually restrained 3 times a day (at approximately 9.00, 13.00, and 17.00 h) for 45 min in transparent plastic cylinders, whilst being exposed to bright light (Van den Hove et al., 2005; Ward and Weisz, 1984). Control (C) pregnant females ($n=8$) were left undisturbed in their home cages. Only litters of 8 or more pups were included in this study. Litters were culled to 8 pups if necessary. A maximum of 2 male and female pups per litter were examined to prevent litter effects (Chapman and Stern, 1978).

At postnatal day 21 (P21), pups were weaned and group-housed for further examination (2 male or 2 female rats/cage; $n=14$ rats per experimental condition per sex). Rats were kept at a reversed day-night cycle from this point onwards (lights on from 17.00-5.00 h). Anxiety- and depression-related behavior of the rats was analyzed from P120 onwards (in the order as discussed below). Subsequently, at P143, plasma corticosterone secretion was assessed. One week later, at P150, the animals were killed by quick decapitation, after which the brains were removed. The hippocampus and FC were dissected, weighed and bilateral tissue samples were placed in a single tube and snapshot frozen in liquid nitrogen after which they were stored at -80 °C until further analysis.

2.2. Anxiety- and depression-related behavior

The elevated zero maze (EZM) introduced by Shepherd et al. (1994) consisted of a circular alley (diameter of 100 cm; path width 10 cm) made from black plastic material that was transparent for infrared light and elevated 20 cm above the floor. The maze was divided into four parts, i.e., two opposite open parts and two opposite closed parts with sidewalls 30 cm in height. The open parts had borders with a height of 5 mm to prevent the rat from stepping down from the apparatus. For the test, the rat was placed into one of the open

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