



Evidence of female-specific glial deficits in the hippocampus in a mouse model of prenatal stress

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Abstract

Prenatal stress (PS) has been associated with an increased incidence of numerous neuropsychiatric disorders, including depression, anxiety, schizophrenia, and autism. To determine the effects of PS on hippocampal-dependent behaviour hippocampal morphology, we examined behavioural responses and hippocampal cytoarchitecture of a maternal restraint stress paradigm of PS in C57BL6 mice. Female offspring only showed a reduction in hippocampal glial count in the pyramidal layer following PS. Additionally, only PS females showed increased depressive-like behaviour with cognitive deficits predominantly in female offspring when compared to males. This data provides evidence for functional female-specific glial deficits within the hippocampus as a consequence of PS.

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1. Introduction

The human brain is highly vulnerable to stressors during foetal development. Recent human studies have demonstrated that

exposure of a pregnant woman to prenatal stress (PS) may impair biological and behavioural responses in their offspring in later life (Weinstock, 2008). This includes an increased vulnerability to neuropsychiatric disorders in later life such as anxiety (Beydoun and Saftlas, 2008), depression (Beydoun and Saftlas, 2008; Maccari et al., 2003), autism (Kinney et al., 2008) and schizophrenia (Koenig et al., 2002).

PS in rodents is accompanied by an hyper-reactive hypothalamo–pituitary–adrenal (HPA) axis (Maccari et al., 1995; Morley-Fletcher et al., 2003) that is thought to cause an increase in anxiety (Vallee et al., 1997; Van den

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Hove et al., 2006b), learning and memory deficits (Hayashi et al., 1998; Vallee et al., 1999) as well as an increased depressive-like behaviour in later life (Alonso et al., 1999; Morley-Fletcher et al., 2003; Secoli and Teixeira, 1998). Such altered reactivity of the HPA axis following PS is thought to involve an enhanced release of glucocorticoid hormones which subsequently enter the foetal circulation to influence foetal brain development (Huizink et al., 2004; Weinstock, 2001). It is hypothesized that activation of such a stress response mid-gestation increases the risk for the aforementioned neuropsychiatric disorders. Nonetheless, impact of PS on the postnatal development of such disorders is not fully understood.

PS also has an impact on cellular morphology and synaptic plasticity. Animal studies of PS have shown a reduction in hippocampal cell proliferation (Fujioka et al., 2006; Koo et al., 2003; Lemaire et al., 2000), hippocampal volume (Coe et al., 2003), synapses (Hayashi et al., 1998) and granule cell number (Schmitz et al., 2002). Glucocorticoid exposure has also been shown to cause reductions similar to those found following PS such as a reduction in hippocampal volume, dendritic length and number of dendritic branch points as well as synapse number (Tata and Anderson, 2009).

Much of the animal research studies for sexual dimorphism in PS have generated mixed results. While sex-specific effects of PS on anxiety (Lemaire et al., 2000; Zagron and Weinstock, 2006), depression (Frye and Wawrzycki, 2003), cognition (Lemaire et al., 2000; Vallee et al., 1999) and cell proliferation (Zuena et al., 2008) has been documented, the sex-specific effects of PS appear to be dependent on the species, strain and age of the offspring used as well as the type and duration of the stressor in PS rodent models (Lemaire et al., 2000; Mueller and Bale, 2006, 2007, 2008; Schmitz et al., 2002; Vallee et al., 1997; Zagron and Weinstock, 2006). The timing of the prenatal stressor may be important to the type of disorder that precipitates as stress during the last weeks of gestation is already associated with the development of schizophrenia in later life (Koenig et al., 2005, 2002).

Human studies have reported glial cell deficits in the anterior cingulate cortex of subjects with schizophrenia (Stark et al., 2004) and depression (Cotter et al., 2001a) as well as in the dorsolateral prefrontal cortex (Cotter et al., 2002) and hippocampus (Muller et al., 2001) of depressive patients. Animal studies have further reinforced these findings with glial pathology found in animal models of depression (Banasr et al., 2008; Gosselin et al., 2009) and chronic stress models (Leventopoulos et al., 2007). Additionally, glial loss has also been found to induce depressive behaviours similar to those observed in animal models of stress (Banasr and Duman, 2008). It is interesting to hypothesize that glial cell deficits, secondary to PS exposure, may contribute to the development of neuropsychiatric disorders in later life.

In the present study, we examined the long-lasting effects of late stage PS in C57BL6 mice on hippocampal morphology and hippocampal-dependent behaviour. Given the recent studies showing stress effects on (i) glial numbers and (ii) sexual dimorphism, we analysed glial cell numbers within the hippocampus in male and female offspring following PS.

2. Experimental procedures

2.1. Animals and prenatal stress

For this study, acclimatised normal C57BL6 mice and their offspring (Charles River, Maastricht, The Netherlands) were used. This study was approved by the Animal Ethics Board of the University of Maastricht, The Netherlands. The animals were housed individually within a temperature-controlled environment (21 ± 1 °C) with 12-hour light/12-hour dark cycle (lights on from 7.00 h) and standard rat chow and water available ad libitum. Pregnancy was determined by observation of vaginal plugs (embryonic day 0 – E0). PS (n=8) was performed daily during the last part of pregnancy (E13–E17) by restraining the dams in transparent 500 ml glass cylinders filled up to a height of 5 mm with water, whilst being exposed to bright light, 3 times daily, 45 min per session (adapted from Van den Hove et al., 2006b). Control pregnant females (n=8) were left undisturbed in their home cages. Animals used for behavioural examination were housed in sibling pairs after weaning under a reversed day–night cycle (12-hour light/12-hour dark cycle; lights on from 19.00 h). No more than two male and/or two female pups per litter were used for each set of experiments to prevent litter effects (Chapman and Stern, 1979).

2.2. Quantitative morphometry

At postnatal day 25 (P25), pups used for quantitative morphometry were quickly decapitated (at 11.00 h) and whole brains were fixed in 4% paraformaldehyde for 4 days and cryoprotected in 24-hour steps of 10%, 20% and 30% sucrose at 4 °C. Brains (n=12 control and PS offspring per sex) were serially sectioned in the coronal plane at 60 µm and sections were stained with cresyl violet using standard methods (Cotter et al., 2001a). Systematic random sampling was carried out with every 5th section of the hippocampus from each brain. All assessments were carried out by a single investigator (ÁB), blind to group status using the Image Pro Plus 5.1 programme (Media Cybernetics, MD, USA). All analysis was carried out on a Leica DM2500 microscope (Leica Microsystems, Ireland), a JVC KY-F550E colour camera (Media Cybernetics, UK) and a Prior 100x x-, y- motorized stage and stage controller (Media Cybernetics, UK) attached to a Heidenhain z-axis depth gauge (Heidenhain, Germany).

The volume of the hippocampal formation was estimated using the Cavalieri principle (Gundersen et al., 1988) and the point counting method. Hippocampal images were captured at low magnification (5×) and cross-sectional areas were measured by outlining the boundaries of (i) the hippocampal formation, (ii) the pyramidal cell layer and (iii) the granule cell layer.

For the whole hippocampus, the density and somal volumes of pyramidal neurons and glial cells in the pyramidal cell layer and granule cells in the dentate gyrus were determined using stereologically based methods (see Fig. 1). These methods and standard criteria for the identification of Nissl-stained neurons and glia were carried out as described previously (Cotter et al., 2001a; Pennington et al., 2008) (see Fig. 1).

Stereology-Pro 2.5 (Kinetic Imaging, Liverpool, UK) was used to measure cell density using the optical disector method (Gundersen et al., 1988). For each field of interest, neurons and glia, number glial nuclear size and neuronal somal size were assessed using the nucleator (Gundersen et al., 1988). Using the optical disector, cell size and count was recorded for 1811 cells yielding an average of 1238 pyramidal neurons, 234 glial cells and 339 granule cells per case. The CE for all estimates in C57BL6 offspring were less than 5%.

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