Frontiers in Neuroendocrinology 41 (2016) 114–128

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

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

The maternal brain under stress: Consequences for adaptive peripartum plasticity and its potential functional implications

David A. Slattery [a], Katharina M. Hillerer [b,*]

[a] Department of Behavioural and Molecular Neurobiology, University of Regensburg, Regensburg, Germany
[b] Department of Obstetrics and Gynaecology, Salzburger Landeskrankenhaus (SALK), Paracelsus Medical University, Salzburg, Austria

ARTICLE INFO

Article history:
Received 17 September 2015
Received in revised form 22 January 2016
Accepted 27 January 2016
Available online 30 January 2016

Keywords:
Neurogenesis
Stress
Corticosterone
Estrogen

ABSTRACT

The peripartum period represents a time during which all mammalian species undergo substantial physiological and behavioural changes, which prepare the female for the demands of motherhood. In addition to behavioural and physiological alterations, numerous brain regions, such as the medial prefrontal cortex, olfactory bulb, medial amygdala and hippocampus are subject to substantial peripartum-associated neuronal, dendritic and synaptic plasticity. These changes, which are temporally- and spatially-distinct, are strongly influenced by gonadal and adrenal hormones, such as estrogen and cortisol/corticosterone, which undergo dramatic fluctuations across this period. In this review, we describe our current knowledge regarding these plasticity changes and describe how stress affects such normal adaptations. Finally, we discuss the mechanisms potentially underlying these neuronal, dendritic and synaptic changes and their functional relevance for the mother and her offspring.

1. Introduction

There is a growing body of literature describing the physiological and behavioural adaptations, which occur across all mammalian species, during the transition from virginity to motherhood. These changes take place at numerous levels, and include neuroendocrine, behavioural, molecular and physiological adaptations, which act in concert to promote reproductive functions and ensure the survival. Thus, the onset of the complex array of maternal behaviours, such as maternal aggression, lactation, and nursing are a direct consequence of these changes. Additionally, towards the end of pregnancy, and into lactation, the response of the hypothalamic–pituitary–adrenal (HPA) axis to a variety of stressors is severely attenuated with a concomitant increase in basal cortisol/corticosterone (Brunton and Russell, 2008; Slattery and Neumann, 2008). Such dampened (re)activity of the HPA axis appears to be essential for the healthy development of the offspring, as high levels of circulating corticosteroids can cross the placenta and have severe consequences on foetal development (Wadhwa et al., 1993). Moreover, there are changes in anxiety-related behaviour, with increased anxiety reported in mid-to-late pregnancy, whereas anxiety is reduced in lactation (Brunton and Russell, 2008; Slattery and Neumann, 2008). There is a growing consensus that these maternal adaptations are not only important for the survival and development of the offspring, but also to protect the mother from the profound hormonal changes that are associated with birth (see below).

In addition to these well-characterised changes, one of the most striking changes that occurs during the peripartum period is a reduction in maternal brain volume; a finding shown in both humans (Oatridge et al., 2002) and rodents (Hillerer et al., 2014). In more detail, Oatridge et al. assessed total brain volume before pregnancy, during pregnancy and up to 13 months postpartum *via* MR imaging. They revealed that brain size was maximally reduced (on average 4.3% or 50.45 cm^3, respectively) during pregnancy, accompanied by an increase in lateral ventricle size, and increased again after birth (Oatridge et al., 2002). Similarly, we were recently able to show that absolute (and relative) brain weights, as well as hippocampal volume were reduced on postpartum day (PD) 14 in rats compared with nulliparous rats (Hillerer et al., 2014).

These observed volumetric changes have been linked to peripartum-associated adaptations in structural and morphological features of maternal neurons since the maternal brain undergoes substantial macroscopic, microscopic, cellular and molecular changes in brain regions that are typically summarised as the "maternal circuitry" (Numan, 2007). This includes the maternal motivational system, which is comprised of brain regions such as the

* Corresponding author at: Perinatal Research Unit, Department of Obstetrics and Gynaecology, Salzburger Landeskrankenhaus (SALK), Müllner Hauptstrasse 48, 5020 Salzburg, Austria.

http://dx.doi.org/10.1016/j.yfrne.2016.01.004
0091-3022/

bed nucleus of the stria terminalis (BNST) and the medial preoptic area (MPOA), the non-specific motivational system including the nucleus accumbens (NAc), the ventral tegmental area (VTA), the olfactory bulb (OB), the medial amygdaloid nucleus (MeA), the anterior hypothalamic nucleus (AHN), the periaqueductal grey (PAG) and the paraventricular and supraoptic nuclei of the hypothalamus (PVN and SON, respectively). This "maternal circuitry", which is conserved across mammals (for review see Swain, 2011), interconnects with the limbic system and the medial prefrontal cortex (mPFC). All of these regions are crucially involved in different aspects of maternal behaviour. It is speculated that these alterations in neuronal plasticity, dendritic morphology and spine characteristics, are necessary for the new mother to deal with the increasing demands of her novel environment. As outlined above, numerous regions within the hypothalamus undergo substantial peripartum plasticity, including glial retraction, altered dendritic length and branching, as well as altered number of axo-somatic and axo-dendritic synapses on oxytocin neurons, these findings have been expertly summarised in numerous reviews. Therefore, we would direct the interested reader to the following reviews (Hillerer et al., 2014; Langle et al., 2002; Oliet and Bonfardin, 2010; Theodosis et al., 2006) and within this review discuss other regions in more detail.

In this review we initially describe our current understanding of peripartum-associated changes in adult neurogenesis, synaptic plasticity and dendritic morphology; focusing particularly within the OB, amygdala, hippocampus and NAc. Thereafter, given the significant impact of stress on different aspects of neural plasticity in both males and females (for reviews see Galea et al., 2014; McEwen, 2013; Pawluski et al., 2015), we focus on the effects of repeated/chronic stress and corticosterone (CORT) exposure on these different forms of neural plasticity during the peripartum period. In the final sections, potential mechanisms underlying such basal- and stress-induced plasticity changes, as well as their functional implications are discussed.

2. Neurogenesis across the peripartum period

In the mammalian brain, there are two main areas that exhibit a high degree of adult neurogenesis throughout life, namely the granule cell layer (GCL) of the dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricles. Generally, neurogenesis consists of four main stages, namely cell proliferation, migration, differentiation and survival of cells, which can be visualised by the use of specific endogenous or exogenous proteins/markers. Factors that affect cell proliferation are those that either suppress or induce mitosis in precursor cells, whereas factors that affect survival promote or prevent the differentiation and/or maturation of cells into fully integrated adult neurons (for review see van Praag et al., 2002; Zhao and Overstreet-Wadiche, 2008). These different phases of neurogenesis can be affected by endogenous and exogenous factors, such as steroid and peptide hormones (see below), exercise and exposure to acute or chronic stress. Many endogenous factors that have been reported to affect adult neurogenesis and/or hippocampal plasticity also undergo substantial peripartum-associated fluctuations, such as estrogen (E_2), progesterone (PROG), CORT, oxytocin (OXT), prolactin (PRL) (see Brunton and Russell, 2008; Slattery and Neumann, 2008; Hillerer et al., 2012 for review). The changes in these systems are essential for ensuring the survival of the offspring, as well as for the mother's physiological and mental health, and it is becoming apparent that they are intricately linked in the peripartum-associated hippocampal plasticity (see Galea et al., 2014; Pawluski et al., 2015 for review). The broad consensus of the available literature shows that parturition and interaction with the young affects adult neurogenesis in a different manner across neurogenic zones, and that peripartum-associated changes in neural plasticity are dependent on time, species and the number of reproductive experiences. In the following sections, unless otherwise stated, the alterations described in neurogenesis in pregnancy and lactation are in comparison with nulliparous controls.

2.1. Hippocampal neurogenesis during pregnancy

There is little convincing evidence that hippocampal cell proliferation is altered during early (Furuta and Bridges, 2005; Pawluski et al., 2010, 2011; Shingo et al., 2003) or late (Furuta and Bridges, 2005; Pawluski et al., 2015, 2010) stages of gestation in rats and mice. For example, neither cell proliferation nor cell survival differed between nulliparous, primiparous or multiparous rats on gestation day (GD)1 (proliferation), when BrdU was injected on the day of mating (Pawluski et al., 2010). Despite the lack of differences in cell proliferation, migration and survival may be altered at specific time points during pregnancy, as increased levels of cell migration and cell survival have been observed in a rat model of hormone-stimulated pregnancy on GD18 (Banasr et al., 2001); although no differences in cell survival were observed on GD21 in pregnant rats (Hillerer et al., 2012). In mice, the number of BrdU+, as well as BrdU+/doublecortin (DCX)+, cells have been shown to be reduced during mid gestation (GD14) (Rolls et al., 2008). This lower survival rate may demonstrate a reduced need of new neurons due to a diminished cell death in very early stages of pregnancy, as revealed by a reduced number of pyknotic cells (i.e. cells that show a pale/absent cytoplasm, darkly stained spherical chromatin, and lack of a nuclear membrane in a cresyl violet staining) in the GCL of rats 24 h after mating (Pawluski et al., 2010). However, it remains open, whether newly generated or old, established neurons are affected by the delayed cell death in the hippocampus and whether this occurs in mice.

2.2. Neurogenesis in the SVZ/OB during pregnancy

Pregnancy has also been shown to significantly affect neurogenesis in the SVZ/OB across pregnancy, with increased cell proliferation in the SVZ observed on GD7 in mice, but not at later time points during gestation (i.e. GD14 and GD21) (Shingo et al., 2003; Larsen and Grattan, 2010). Interestingly, the opposite findings have been described in rats with changes seen later in pregnancy (Furuta and Bridges, 2005). However, the contradictory results might not only be explained by the difference in species, but moreover, by the number of BrdU injections and the amount of BrdU injected (Taupin, 2007), which differed across the studies. Given the fact that the adult-born neurons are integrated in the OB circuitry and show structural and functional plasticity (Altman, 1969) (and see Lledo et al., 2006 for review) it can be speculated that such increased cell proliferation in both rats and mice may enhance synaptic connectivity, when olfactory demands are high and, thereby, contribute to the onset of maternal behaviour.

2.3. Neurogenesis in the SVZ/OB during the postpartum period

Despite the presumed importance of pregnancy-stimulated neurogenesis in the SVZ, there is no study assessing whether lactation itself affects adult neurogenesis in the olfactory system in rodents. However, interaction with the offspring has been demonstrated to affect SVZ neurogenesis during the early postpartum period in sheep. In more detail, Brus et al. showed that cell proliferation is reduced in the SVZ, the main OB, as well as in the DG, two days after parturition. The authors speculated that this may be important to facilitate the perceptual and memory demands associated with maternal behaviour in the early postpartum period by