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BRAIN RESEARCH

Research Report

Callosal oligodendrocyte number in postpartum Sprague-Dawley rats

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ARTICLE INFO

Article history:
Accepted 12 February 2009
Available online 25 February 2009

Keywords:
Gliogenesis
Oligodendrocyte
Corpus callosum
Pregnancy
Postpartum
Lactation
Prolactin

ABSTRACT

Prolactin (PRL), an anterior pituitary hormone with neurogenic properties associated with pregnancy, has been implicated in oligodendrocyte proliferation during gestation, contributing to increased myelination in the maternal brain. However, PRL is elevated during lactation as well, suggesting that the postpartum (PP) period may contribute to additional gliogenesis in lactating females. In the present study, we assessed oligodendrocyte number in the corpus callosum (CC) of female Sprague-Dawley rats near the end of gestation, and at two weeks postpartum in both lactating and non-lactating dams, and in virgins. Though pregnant females did not differ significantly from any other group, lactating females had significantly more oligodendrocytes in the CC than virgins ($p = .01$), and in medial regions of the CC than non-lactating dams ($p < .02$). Oligodendrocyte number in the CC of pregnant and PP females correlated positively with the number of pups in their litter ($r^2 = .68$, $p < .005$). These results suggest that the gestational period contributes to oligodendrocyte proliferation or survival, likely mediated by an endocrine hormone whose concentration varies with the size of the litter. The PP period also contributes to increases in CC oligodendrocyte number, though it is unclear whether endocrine influences and/or pup-interaction underlie the differences in myelination between lactating and non-lactating groups. Further investigation is required in order to confirm whether the effects observed are mediated by members of the PRL-family, experience, and/or other gestational/PP endocrine hormones.

1. Introduction

In rats, the subventricular zone (SVZ) produces multipotential progenitor cells that migrate and differentiate into neurons and glia (Levison and Goldman, 1993). Glial precursors from the SVZ migrate radially during gliogenesis to the corpus callosum (CC) and cerebral cortex, where some differentiate into oligodendrocytes, the myelinating cells of the central nervous system (CNS) (Nait-Oumesmar et al., 1999). Following focal brain injury, post-mitotic oligodendrocytes are unable to provide remyelination (Keirstead and Blakemore, 1997). However local and SVZ progenitors continue to produce oligodendrocytes throughout adulthood (Gensert and Goldman, 1997; Levison et al., 1999), and these cells have been shown to contribute to repair and remyelination after a demyelinating injury (Polito and Reynolds, 2005). The profile of oligodendrocyte myelination varies

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doi:10.1016/j.brainres.2009.02.029

between sexes in rodents, with females possessing fewer myelinated axons in the CC (Kim and Juraska, 1997), and having greater oligodendrocyte turnover in adulthood (Cerghet et al., 2006).

Research suggests that one mechanism subserving the increased oligodendrocyte turnover seen in females may be prolactin (PRL). PRL, produced primarily in the anterior pituitary (Riddle et al., 1933), has been shown to act as an astroglial mitogen (DeVito et al., 1992) and has general neuro- and gliotrophic properties. PRL is involved in glial responses following hypoxic ischemic injury in the rat, and infusion of exogenous PRL is sufficient to facilitate repair in damaged brain areas (Moderscheim et al., 2007). In addition, PRL-mediated neurogenesis during pregnancy leads to significant increases in the number of new cells in the SVZ, and another smaller increase in cell proliferation is seen just after parturition (Shingo et al., 2003).

More recently, research has begun to focus on the role of glial plasticity in the onset and maintenance of maternal behaviour. Primiparous rats display increased numbers of astrocytes in the medial preoptic area, a region critical for maternal behaviour, while in multiparous females astrocyte number is decreased in the medial amygdala (Featherstone et al., 2000). Lactating rats display higher concentrations of glial fibrillary acid protein (GFAP) and basic fibroblast growth factor (bFGF) than virgins or late-term pregnant females (Salmaso et al., 2005), and once this occurs, maintenance of changes in GFAP and bFGF expression is not dependent upon continued suckling stimulation (Salmaso and Woodside, 2006). Taken together, these results are suggestive of a role for both neural and glial plasticity in the expression of maternal behaviour.

Increased oligodendrocyte proliferation and myelination in the CC and spinal cord have been reported in pregnant mice, and these increases were sufficient to repair acute demyelinating damage to the spinal cord (Gregg et al., 2007). In virgin mice, systemic administration of PRL resulted in increased oligodendrocyte proliferation (Gregg et al., 2007), supporting the hypothesis that oligodendrocyte proliferation observed during gestation was mediated by PRL secretion at the onset of pregnancy.

During pregnancy, women with multiple sclerosis (MS), a demyelinating disease of the central and peripheral nervous system, experience a remission of their symptoms proportional to the decrease observed in active white-matter lesions (van Walderveen et al., 1994; Confavreaux et al., 1998; Voskuhl, 2003). PRL mediated oligodendrocyte proliferation has been implicated in this improvement: Gregg et al. (2007) demonstrated that precursor cells that had undergone mitotic division on gestational day 7 in female mice had migrated and differentiated into myelinating oligodendrocytes in the CC by gestation day 18. In addition, these authors found increased myelin density in the genu of the CC at two weeks PP (Gregg et al., 2007), however, there was no examination of the contribution of the PP period to myelination. Since PRL has been implicated in oligodendrocyte proliferation and is elevated during lactation (Freeman et al., 2000), a further examination of the PP period may elucidate whether PRL has similar gliogenic effects after parturition.

The purpose of the present study was to examine the effect of gestation and PP lactation on oligodendrocyte number in the CC of the rat. Oligodendrocytes were assessed near the end of the gestational period (GD18 group) and two weeks postpartum in both lactating (L-PPD14) and non-lactating dams (NL-PPD14). We hypothesized that females near the end of gestation would have higher numbers of oligodendrocytes in the CC than virgins. In addition, it was expected that lactating dams would display more CC myelination than non-lactating PP females.

2. Results

Virgins age-matched to GD18 and PPD14 groups did not differ on any measure and were therefore combined for the remainder of the analyses (called virgins hereafter). Three *a priori* hypotheses were tested using independent samples *t*-tests. It was hypothesized that gestational (GD18) females would display greater numbers of oligodendrocytes in the CC than virgins. It was also predicted that oligodendrocyte number in lactating postpartum females (L-PPD14) would differ from both virgins and non-lactating postpartum animals (NL-PPD14).

There was no significant difference between the mean number of oligodendrocytes in the CC of virgins and GD18 females, however, L-PPD14 animals had a significantly greater mean number of oligodendrocytes than the virgin group ($t=-3.381$, $df=8$, $p=.01$) (Fig. 1B). A trend toward greater oligodendrocyte number in L-PPD14 compared with NL-PPD14 animals did not achieve significance (Fig. 1B).

We suspected that the trend observed between L- and NL-PPD14 groups might represent genuine differences that failed to reach significance as a result of an uneven distribution of new oligodendrocytes. While little research has examined adult oligodendrocyte migratory patterns under normal physiological conditions, during early postnatal development oligodendrocyte precursors appear to migrate to the CC primarily from the dorsolateral SVZ along the lateral ventricular wall (Kakita and Goldman, 1999). This migratory route would lead OPCs to relatively medial regions of the CC in the areas we examined (between +2.28 mm and +1.32 mm anterior to Bregma). Kakita and Goldman (1999) have reported migratory speeds of 53–88 μm/h for these precursor cells, suggesting that over the two week period prior to sacrifice, precursors would be unlikely to migrate very far laterally before differentiating and beginning to express makers of mature oligodendrocytes. Thus, we suspected that group differences might be concentrated in medial regions of the CC. As expected, virgin and L-PPD14 oligodendrocyte counts differed significantly in medial regions (defined as ±1 mm from midline) of the CC ($t=-2.706$, $df=8$, $p<.05$), and L-PPD14 females had significantly higher numbers of oligodendrocytes in the medial CC than NL-PPD14 dams ($t=3.139$, $df=7$, $p<.02$) (Fig. 2). Finally, examination of CNPase-positive cells in the anterior commissure revealed that there were no significant differences in oligodendrocyte number between groups (Fig. 3).

The mean number of oligodendrocytes in the CC of females in GD18, NL- PPD14, and L-PPD14 groups correlated positively