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Research report

Disrupted migration and proliferation of neuroblasts after postnatal administration of angiogenesis inhibitor

Andreas Angelidis[a], Enikő Račeková[a], Petra Arnoul[a], Monika Závodská[a], Adam Raček[b], Marcela Martončíková[a,*]

[a] Institute of Neurobiology, Biomedical Research Center, Slovak Academy of Sciences, Košice, Slovak Republic
[b] Department of Anatomy, Histology and Physiology, University of Veterinary Medicine and Pharmacy in Košice, Slovak Republic

HIGHLIGHTS

- Inhibition of angiogenesis disrupted reorganization of blood vessels in the RMS.
- Impaired vasculature scaffold caused misrouted migration of neuroblasts.
- Disrupted migration resulted in the accumulation of proliferating cells in the RMS.
- Blood vessels reorganization is crucial for regular course of postnatal neurogenesis.

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ABSTRACT

In adult rodents, neuroblasts originating from the subventricular zone migrate tangentially through the rostral migratory stream (RMS) toward the olfactory bulb where they differentiate into interneurons. Neuroblasts in the RMS migrate in chains for a long distance along specifically arranged blood vessels which promote their migration. Although blood vessels in the neurogenic region of the forebrain are present early in development, their rearrangement into this specific pattern takes place during the first postnatal weeks. Here we examined the relevance of this rearrangement to the migration-guiding "scaffold" for the neurogenic processes in the RMS such as cell migration and proliferation. To disturb the reorganization of blood vessels, endostatin – an inhibitor of angiogenesis, was administered systemically to rat pups during the first postnatal week. Ten days or three months later, the arrangement of blood vessels, migration and proliferation of cells in the RMS were assessed. As we expected, the inhibition of angiogenesis disrupted rearrangement of blood vessels in the RMS. The rearrangement's failure resulted in a strong disruption of the mode and direction of neuroblast migration. Chain migration failed and neuroblasts migrated out of the RMS. The inhibition caused a slight increase in the number of proliferating cells in the RMS. The consequences were more obvious ten days after the inhibition of angiogenesis, although they persisted partly into adulthood. Altogether, here we show that the process of rearrangement of blood vessels in the RMS during the early postal period is crucial to ensure the regular course of postnatal neurogenesis.

1. Introduction

The subventricular zone (SVZ) lining the lateral ventricles is the largest neurogenic area in the adult mammalian brain supplying new neurons to the olfactory bulb (OB) throughout life. SVZ-derived neuroblasts initially migrate tangentially along a well-delineated pathway called the rostral migratory stream (RMS). Once the neuroblasts reach the OB they migrate radially to their final positions in the bulbar layers and differentiate into inhibitory interneurons (Altman, 1969; Luskin, 1993). The migration of neuroblasts in the postnatal period strikingly differs from that in the embryonic period. During development, differentiated neurons use radial glia as a physical substrate along which they migrate to their final location. Since radial glia differentiate into astrocytes after birth, they cannot be used any longer as a substrate which promotes migration (Cameron and Rakic, 1991). In the postnatal period, SVZ neuroblasts migrate via the RMS using each other as a cellular substrate, thus creating long chains that are ensheathed with astrocytes (Lois and Alvarez-Buylla, 1994). Besides this specific mode of

* Corresponding author at: Institute of Neurobiology, Biomedical Research Center SAS, Soltesovej 4, 040 01 Kosice, Slovak Republic.
E-mail address: martoncikova@saske.sk (M. Martončíková).

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migration, called homophilic or chain migration, neuroblasts of the RMS are characterized by another unusual feature: they are able to proliferate during migration toward the OB (Menezes et al., 1995). This is in contrast to the neurons generated during embryonic period which begin to migrate as postmitotic (Luskin and Shatz 1985).

An important component of the SVZ stem cell niche is the vasculature. Blood vessels, besides their trophic function, release soluble factors that stimulate neural stem cell self-renewal, inhibit their differentiation and enhance neuron production (Shen et al., 2004). Recent studies have revealed an unsuspected function of blood vessels in the neurogenic region of the adult brain. These studies have demonstrated that blood vessels in the SVZ, RMS and OB serve as a migration promoting scaffold for neuroblasts (Bovetti et al., 2007a; Whitman et al., 2009; Snapyan et al., 2009; Martončíková et al., 2014) as well as a source of migratory cues (Snapyan et al., 2009). Indeed, the RMS is characterized by specific arrangement of blood vessels in contrast to the rather random orientation of blood vessels elsewhere in the brain (Whitman et al., 2009; Snapyan et al., 2009; Martončíková et al., 2014). Our previous results suggest that the pattern of vasculature in the RMS is species specific (Martončíková et al., 2014). In adult mice, blood vessels are aligned parallel to the migratory pathway (Whitman et al., 2009). However, in adult rats, such parallel orientation of blood vessels is only in the rostral part of the RMS, while in its caudal part their orientation is mostly orthogonal or oblique to the RMS (Martončíková et al., 2014). Although association between blood vessels and migrating neuroblasts of adult rodents has been shown (Bovetti et al., 2007a; Whitman et al., 2009; Snapyan et al., 2009), Nie et al. (2010) have found no evidence for preferential juxta-position of migratory doublecortin-positive neuroblasts and vasculature in the neonatal (P2 and P4) RMS. It might be explained by highly dynamic changes during neonatal period. Astrocytes, closely associated with blood vessels, are also components of the migratory scaffold and are an important partner in the vasculature-guided migration (Whitman et al., 2009). The Saghatelyan group has provided a functional and mechanistic explanation of the vasculature-guided migration of neuroblasts in the adult brain. They hypothesized that vasculature-mediated migration of neuroblasts from the SVZ to the OB is controlled by the dynamic interactions among neuroblasts, astrocytes and endothelial cells. Brain-derived neurotrophic factor (BDNF) produced by endothelial cells fosters the entrance of neuroblasts into the migratory phase. This action is mediated by p75NTR, a low-affinity receptor for BDNF on neuroblasts. Then, GABA released from neuroblasts induces the insertion of high-affinity TrkB receptors on astrocytes which trap extracellular BDNF and thus foster the entry of migrating neuroblasts to the stationary phase. The authors suggested that the periodicity of the migratory and stationary phases results in movement of neuroblasts (Snapyan et al., 2009).

Although the vascular network in the forebrain neurogenic region is present from the very early phase of development (Colín-Castelán et al., 2011), reorganization of blood vessels into the migration-promoting scaffold in the RMS takes place during the early postnatal period. This reorganization is controlled by astrocytes emerging in the outer border of the RMS via vascular endothelial growth factor (VEGF) signaling (Bozoyan et al., 2012). According to the above findings, the reorganization of blood vessels during the early postnatal period seems to be essential for the formation of the proper migratory scaffold. The aim of our study was to examine how inhibition of angiogenesis during the first postnatal days influences the arrangement of blood vessels into the migratory scaffold and whether this might consequently affect neurogenic processes, such as the proliferation and migration of neuroblasts in the RMS. To this end, the endogenous inhibitor of angiogenesis - endostatin was administered to rat pups during the first postnatal week, the time of vasculature rearrangement.

The effect of inhibition of angiogenesis on blood vessel arrangement, migration and proliferation of neuroblasts in the RMS was assessed at two survival times: ten days or three months after the inhibition. We found that inhibition of angiogenesis during the early postnatal period disturbed the reorganization of blood vessels into their proper arrangement. This caused striking disruption in neuroblast migration in terms of mode and direction. Chain migration failed and neuroblasts migrated out of the RMS. These consequences were more apparent ten days after the inhibition of angiogenesis. In addition, we revealed an increased number of proliferating cells in the RMS which was more profound three months after the angiogenesis inhibition. Taken together, our results suggest that not only establishment of vasculature, but the reorganization of blood vessels in the RMS during the early postnatal period is crucial for the regular course of postnatal neurogenesis.

2. Results

To examine whether suppression of vasculature rearrangement could influence proliferation and migration of cells in the RMS, we induced inhibition of angiogenesis with endostatin during the first five postnatal days. The impact of angiogenesis inhibition on the blood vessels' arrangement as well as proliferation and migration of cells in the RMS was assessed after short and long survival times, ten days or three months later, respectively. The assessment was performed in three anatomical parts of the RMS: the vertical arm – the segment arising from the SVZ, positioned between the corpus callosum and striatum; the elbow – the most ventral, bent segment of the RMS; and the horizontal arm reaching rostrally toward the OB (Fig. 1A).

2.1. Arrangement and density of blood vessels in the RMS ten days after inhibition of angiogenesis

On the postnatal day 15 (P15), i.e. ten days after inhibition of angiogenesis, we did not observe conspicuous morphological differences in the arrangement of the RMS blood vessels in the experimental animals in comparison with the age-matched control rats. At this time, the rearrangement of blood vessels into the typical pattern is still under development, so it is difficult to notice particular differences between experimental and control rats. In both groups of rats, blood vessels in the vertical arm of the RMS, were oriented at distinct angles with respect to the migratory pathway (Fig. 1B, B′), while in the elbow and the horizontal arm they were oriented mostly in parallel (Fig. 1C, C′). However, we observed that the blood vessels in the RMS of the experimental group were situated rather along the border of the migratory pathway (Fig. 1C), while in the control group they were also situated in the center of the RMS (Fig. 1C′). In addition, in some brain sections of experimental rats, many vessels at the border of the elbow and the horizontal arm had medio-lateral orientation (Fig. 1D). Morphological observations were followed by quantitative analyses. We counted blood vessel density and branching points of vessels on coronal sections and sagittal sections, respectively. The density of blood vessels in each part of the RMS of the experimental group was slightly increased compared to the control group, but it was not statistically significant (Fig. 2H, control group (C) versus experimental group – angiogenesis inhibition (AI): vertical arm: C 265.7 ± 11.8 vs AI 296.3 ± 26.5; elbow: C 385.5 ± 8.4 vs AI 442.2 ± 55.9; horizontal arm: C 263.3 ± 16.3 vs AI 295.7 ± 26.3 per mm^2).

However, quantification of the number of blood vessel branching points revealed that inhibition of angiogenesis caused significant increase in the branches in all parts of the RMS (Fig. 1I, control group (C) versus experimental group – angiogenesis inhibition (AI): vertical arm: C 3.0 ± 0.9 vs AI 10.3 ± 0.8; elbow: C 2.4 ± 0.9 vs AI 8.7 ± 1.2; horizontal arm: C 2.3 ± 1.0 vs AI 4.9 ± 0.8; Student's *t*-test, $p < 0.05$ for the horizontal arm, $p < 0.001$ for the vertical arm and the elbow).

2.2. Migration of neuroblasts ten days after angiogenesis inhibition

Ten days after inhibition of angiogenesis, the chain migration of

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