Regulation of postnatal neurogenesis and brain angiogenesis by thyroid hormone

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, mondagen den 14 december 2009 kl.13:00

av

Jenny Liqun Zhang

Fakultetsopponent: Professor Sebastian Jessberger

Institute of Cell Biology, ETH-Hönggerberg, Zürich, Switzerland

Avhandlingen baseras på följande delarbeten:

Paper I: **Liqun Zhang**, Klas Blomgren, H. Georg Kuhn, Christi M. Cooper-Kuhn

Effect of postnatal thyroid hormone deficiency on neurogenesis in the juvenile and adult rat

Neurobiology of Disease **(2009) 34: 366-374**

Paper II: **Liqun Zhang**, Christi M. Cooper-Kuhn, Ulf Nannmark, Klas Blomgren, H. Georg Kuhn

In vivo and *in vitro* effects of thyroid hormone on brain angiogenesis

Published online by the *Journal of Cerebral Blood Flow and Metabolism* (Nov. 2009)

Paper III: Liqun Zhang, Klas Blomgren, H.Georg Kuhn

Astrocytes stimulated by thyroid hormone promote hippocampal neural stem cell growth and neuronal differentiation

Submitted

GÖTEBORGS UNIVERSITET

Regulation of postnatal neurogenesis and brain angiogenesis by thyroid hormone

Jenny Liqun Zhang
CBR, Institute for Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Sweden

Abstract
Thyroid hormone (TH), which is secreted by the thyroid gland, exerts significant effects on the central nervous system (CNS), especially during development, so that delayed treatment of perinatal hypothyroidism results in severe cognitive retardation. Continuous postnatal neurogenesis occurs throughout adulthood in the subventricular zone (SVZ) of the lateral ventricle wall and in the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampal formation. The neural stem cells in these regions undergo proliferation, migration, differentiation into functional neurons, and integration into neural networks. These two highly specialized regions are termed 'neurogenic niches', which mainly contain neural stem cells, endothelial cells, astrocytes, and microglial cells. In the SVZ, there are also ependymal cells. Many factors, including growth factors and hormones, have been implicated in the regulation of neurogenesis.

The overall aim of this thesis was to investigate the effects of TH on the different cell types, including neural stem cells, endothelial cells and astrocytes, in two neurogenic niches. A postnatal hypothyroidism rat model was set up by adding PTU to the drinking water from Postnatal Day 1 (P1) to P21. We studied the acute and long-term effects of postnatal TH deficiency (PTHD) on both neurogenesis and angiogenesis in the SVZ and dentate gyrus.

In **Paper I**, we show region-dependent responses to PTHD. The proliferation of neural stem cells and the total number of granule neurons in the dentate gyrus were significantly reduced in PTHD rats at P21, whereas no effects on the SVZ/OB system, as compared with control rats. In addition, after the withdrawal of PTU at P22, hippocampal neurogenesis increased as a result of increased cell survival. These changes were paralleled by alterations in the gene expression patterns of growth factors and apoptotic factors, i.e., *Fgf2, Ngf, Wnt3a, Vegfa and Bcl2*, at both P21 and P90.

In **Paper II**, we describe a reduction in angiogenesis at P21 due to PTHD, as evidenced by reductions in the complexity and density of the microvessels, both in the neocortex and dentate gyrus. However, these defects were fully recovered by P90, following PTU withdrawal at P22. In the neocortex, these changes were paralleled by altered levels of VEGFA and FGF2. Furthermore, we report that the physiologic concentration of TH promotes proliferation and tube-like structure formation, and inhibits the death of brain-derived endothelial (RBE4) cells *in vitro*.

In **Paper III**, we investigate the region-specific contribution of astrocytes to the activities of neural stem cells after T3 (50 nM) treatment. Conditioned medium (CM) was collected from cultures of SVZ and hippocampal astrocytes after T3 (50 nM) treatment, and was added to the cultures of neural stem cells (NSCs) from the corresponding brain regions. The CM from T3-treated hippocampal astrocyte cultures promoted hippocampal NSCs survival by increasing the proliferation and decreasing the cell death, whereas the CM from T3-treated SVZ astrocyte cultures did not have similar effects on the activities of the SVZ NSCs. Interestingly, the migration of neuroblast from both SVZ and hippocampus was significantly increased after culturing with CM after T3-treatment from corresponding regions. Furthermore, the astrocytes after T3-treatment from these two regions displayed different expression patterns for the *Bdnf, Noggin, Wnt3a, Pedf*, and *Thrb* genes, which are implicated in the regulation of neurogenesis.

In summary, this thesis demonstrates the hyper-susceptibility of hippocampal neurogenesis to PTHD including NSCs and astrocytes, and provides evidence of a strong linkage between brain angiogenesis and thyroid hormone levels.

Key words: thyroid hormone, neurogenesis, angiogenesis, SVZ/OB, hippocampus, neural stem cells, endothelial cells, astrocytes

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