NEURAL STEM/PROGENITOR CELLS IN THE POST-ISCHEMIC ENVIRONMENT:
Proliferation, Differentiation and Neuroprotection

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av

Jonas Faijerson

Fakultetsopponent:
Docent Yvan Arsenijevic, Hôpital Ophtalmique Jules Gonin, Lausanne, Schweiz

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II. Faijerson J., Anderson M.F., Apricó K., Nilsson M., Eriksson P.S. and Komitova M.
Gene expression profiling in the perifocal neocortex after experimental stroke in rats: TRH up-regulation and effects on adult neural stem/progenitor cells. In manuscript.

III. Tinsley R.B.*, Faijerson J.* and Eriksson P.S.

Adult neural stem/progenitor cells reduce excitotoxicity via pentinin, a novel neuroprotective peptide. In manuscript.

*Equal contribution.
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Jonas Faijerson
Institute of Neuroscience and Physiology, Göteborg University, Göteborg, Sweden, 2007

Abstract
Stroke is one of the leading causes of chronic disability and death in the Western world. Today, no 
treatment can repair the cellular loss associated with an ischemic lesion. However, the discovery and 
dynamic regulation of neural stem/progenitor cells in the adult mammalian brain has resulted in exciting 
opportunities for future therapeutic interventions. Endogenous or grafted neural stem/progenitor cells are 
activated following an ischemic insult. These cells undergo directed migration towards infarcted areas, 
and differentiate in response to the insult. Unfortunately, the results of this regenerative effort are limited 
compared to the amount of tissue loss. This could be due to low survival of the recruited cells, but could 
also be explained by insufficient activation or dysfunctional lineage selection. Whether the lineage 
selection of neural stem/progenitor cells is altered following a lesion in the brain, what signals that are 
responsible for their activation or whether these cells can participate in post-lesion regeneration, 
astrogliosis or neuroprotection have yet to become clear. A greater understanding of these processes is 
necessary for finding ways to improve the endogenous regenerative capacity.

We found that reactive astrocytes, a prominent part of the post-ischemic environment, induced astroglial 
differentiation of adult neural stem/progenitor cells in vitro. Moreover, astrocytes derived from these cells 
were shown to participate in glial scar formation in vitro.

After studying gene expression in the peri-infarct region following focal ischemia, the expression of 
several genes was induced. We chose to focus our attention on one of these genes and its product, 
thyrotropin-releasing hormone (TRH). Immunoreactivity for TRH was found in several areas in both 
lesioned and intact brain regions, including in microglia present in the areas surrounding the lesion. 
Furthermore, TRH receptors were expressed on cultured neural stem/progenitor cells and TRH potently 
induced the proliferation of these cells. TRH is an interesting target for stroke treatment, but it also has 
many central effects in the brain and systemic administration may prove problematic. An interesting 
protocol for local delivery of TRH would be by grafting stem/progenitor cells, genetically engineered to 
secrete the peptide. In order to create a foundation for neuroprotective gene therapy, we developed 
efficient methods for non-viral transfection of neural stem/progenitor cells.

Since neural stem/progenitor cells migrate towards the ischemic area we wanted to investigate whether 
these cells secreted factors that could protect neurons against excitotoxicity, the main inducer of cell 
death following a stroke. Mass spectrometric analysis of factors secreted from cultured neural 
stem/progenitor cells led to the identification of a novel neuroprotective peptide, which we termed 
pentinin. This peptide potently reduced excitotoxicity in both mature and immature neurons in an ex vivo 
hippocampal slice model.

The results presented in this thesis show that the proliferation and differentiation of neural 
stem/progenitor cells can be dramatically affected by factors in the post-ischemic environment. 
Furthermore, the results suggest that neural stem/progenitor cells can participate in both glial scar 
formation and neuroprotection after an ischemic lesion. Finally, a novel neuroprotective peptide was 
identified. This peptide may be important for the protection of endogenous cells following insults in the 
brain and may represent an effective novel target for the treatment of stroke.

Keywords: Neural stem cells, neural progenitor cells, stroke, ischemia, reactive astrocytes, astrogliosis, 
proliferation, differentiation, neurogenesis, excitotoxicity, transfection, neuroprotection