# Brain Regeneration

*in vitro* and *in vivo* studies of exercise-related effects on brain plasticity

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Göteborgs universitet kommer att offentligen försvaras i föreläsningssal Karl Kylberg, Medicinaregatan 7, fredagen den 16 maj 2008 kl. 13.00

**av**


## Cecilia Bull


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Professor Pamela E. Knapp,
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The thesis is based on the following papers:

**I.** **Persson A.I.*, Bull C.* and Eriksson P. S.** Requirement for Id1 in opioid-induced oligodendrogenesis in cultured adult rat hippocampal progenitors. *Eur. J. Neurosci.* 23, 2277-2288 (2006).

**II.** **Naylor S. A.*, Bull C.*, Nilsson M., Zhu C., Björk-Eriksson T., Eriksson P. S., Blomgren K., and Kuhn H. G.** Voluntary running rescues adult hippocampal neurogenesis after irradiation of the young mouse brain. *Submitted for re-revision to Proceedings of the National Academy of Science, (PNAS).*

**III.** **Bull C., Naylor A., Lindahl V., Grandér R., Alborn A., Persson A. I., Björk-Eriksson T., Blomgren K. and Cooper-Kuhn C.** Effects of physical activity on oligodendrocytes in the corpus callosum after irradiation of the postnatal mouse brain. *Manuscript.*

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*in vitro* and *in vivo* studies of exercise-related effects on brain plasticity

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## ABSTRACT

Neural stem and progenitor cells in the germinal regions of the adult brain, such as the hippocampus, are of great interest, because they provide the possibility for enhanced brain plasticity or can contribute to endogenous cell replacement after injury or disease. Voluntary exercise was recently shown to robustly induce cellular and structural plasticity, thereby contributing to overall brain health. This thesis focuses on exercise-related effects on cell genesis of neurons and oligodendrocytes *in vitro* and *in vivo.* In Paper I, we demonstrated that the exercise-induced, endogenously released opioid peptide □-endorphin enhanced oligodendrogenesis in adult hippocampal progenitors *in vitro.* Results revealed a requirement for the helix-loop helix transcriptional regulator "Inhibitor of Differentiation" (Id) 1 in opioid-induced oligodendrogenesis. In Paper II, we studied the effects of voluntary exercise during adulthood on neurogenesis and behavior, subsequent to irradiation in the young mouse brain. Voluntary exercise following irradiation restored the hippocampal stem cell pool, increased neurogenesis, and ameliorated irradiation-induced alterations in behavior. Moreover, orientation of immature neurons in the hippocampal dentate gyrus was perturbed after irradiation; however, voluntary exercise restored proper orientation. In Paper III, we proceeded to investigate potential effects of voluntary exercise on oligodendrogenesis after irradiation to the immature brain. We demonstrate an efficient irradiation-induced reduction in the total number of Olig2-positive cells of the corpus callosum, considered to be mainly oligodendroglial cells, without affecting the number of newborn glial progenitor cells. Our results also reveal that, in contrast to the beneficial effects of exercise on neurogenesis in the hippocampus, voluntary running does not seem to affect cell proliferation or oligodendrogenesis in the corpus callosum.

In conclusion, this thesis demonstrates the usefulness of physical exercise for functional and structural brain recovery, with special emphasis on insults to the juvenile brain. In addition, these results highlight the capacity of the adult brain to regenerate through activation of endogenous neural progenitors and stem cells.

Keywords: brain, neural progenitor cells, stem cells, hippocampus, corpus callosum, rat, mouse, regeneration, neurogenesis, oligodendrogenesis, irradiation, exercise

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