

# Inflammation and Cell Proliferation Following Perinatal Brain Injury

Katarina Järlestedt

Perinatal Center, Department of Physiology, Institute of Neuroscience and Physiology,  
The Sahlgrenska Academy, University of Gothenburg, Box 432, 405 30 Gothenburg, Sweden

## Abstract

Inflammation plays an important role in cerebral ischemic injury in the immature brain. The aim of the thesis was to investigate (1) the role of astrocyte activation and reactive gliosis in neonatal hypoxic-ischemic (HI) brain injury, (2) the role of complement derived peptide C3a in neonatal HI brain injury, (3) the effect of neonatal HI brain injury on fear learning and behaviour, (4) the effects of lipopolysaccharide (LPS) induced systemic inflammation on cell proliferation in the developing brain. Glial fibrillary acidic protein and vimentine deficient (*GFAP<sup>-/-</sup>Vim<sup>-/-</sup>*) mice, transgenic mice over-expressing C3a under the control of a GFAP promoter (*C3a/GFAP*) and wild type mice were exposed to HI at postnatal day 9 (P9). To induce unilateral HI, the left common carotid artery was permanently ligated followed by exposure to a gas mixture of low oxygen content. Bromodeoxyuridine (BrdU) was injected intraperitoneally (i.p.) to detect cell proliferation. Memory was tested in mice exposed to HI by using a trace fear conditioning test. We found no difference in the hemisphere or infarct volume between *GFAP<sup>-/-</sup>Vim<sup>-/-</sup>* and wild-type mice 3 and 22 days after HI. However at P31, *GFAP<sup>-/-</sup>Vim<sup>-/-</sup>* mice showed an increase in NeuN<sup>+</sup>BrdU<sup>+</sup> (surviving newly born) neurons in the ischemic cortex compared to wild-type. *C3a/GFAP* mice had reduced loss of hippocampal volume in the ipsilateral compared to the contralateral hemisphere and a higher hippocampus/hemisphere ratio compared to the WT in the ipsilateral hemisphere. *C3a/GFAP* mice showed a higher number of newly born and surviving neurons, astrocytes and microglia in the dentate gyrus in the ischemic hemisphere compared to the wild type mice. However, a reduced number of astrocytes and microglial cells were found in the *C3a/GFAP* mice in the ipsilateral hemisphere compared to wild-type mice. C3a mRNA expression increased in the ipsilateral subventricular zone, hippocampus and cortex in *C3a/GFAP* and wild-type neonatal mice between 0 to 6 hours after HI as shown with real time-PCR. Injection of C3a peptide into the ipsilateral cerebral ventricle, in wild-type mice, 1 hour after HI, improved memory function. The trace fear conditioning test with a shock-paired tone and light showed that the control mice remembered the shock-paired context and the shock-paired light and tone while HI treated mice did not. The volume of the ipsilateral hippocampus and the amygdala was reduced in wild-type mice exposed to HI. Wild type mice injected i.p. with LPS on P9 and evaluated at P40 showed that LPS reduces cell proliferation and survival of neurons and astrocytes in the developing brain.

Conclusion: Reactive gliosis and LPS-induced systemic inflammation have negative effects on neurogenesis and cell proliferation; whereas the complement derived peptide C3a improves the outcome after neonatal HI. Early targeting treatments that increase cell survival may be important after neonatal HI and C3a could be such a potential therapeutic target in the future.

**Key words:** hypoxia-ischemia, immature brain, reactive gliosis, complement system, C3a, fear conditioning, lipopolysaccharide, inflammation

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### **Katarina Järlestedt**

Opponent: Dr. David W. Walker  
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Monash Medical Center, Australia

Avhandlingen baseras på följande delarbeten:

- I. Attenuation of reactive gliosis does not affect infarct volume in neonatal hypoxic-ischemic brain injury in mice**  
Katarina Järlestedt\*, Catherine I. Rousset\*, Maryam Faiz, Ulrika Wilhelmsson, Anders Ståhlberg, Hana Sourkova, Marcela Pekna, Carina Mallard, Henrik Hagberg and Milos Pekny.  
*PLoS ONE, 2010, April, 5, 4*
- II. Complement-derived peptide C3a is neuroprotective in neonatal hypoxic-ischemic brain injury**  
Katarina Järlestedt, Catherine I. Rousset, Anders Ståhlberg, Hana Sourkova, Alison L. Atkins, Scott R. Barnum, Milos Pekny, Carina Mallard, Henrik Hagberg and Marcela Pekna (*manuscript*)
- III. Pavlovian fear conditioning detects hypoxic-ischemic brain injury in neonatal mice**  
Katarina Järlestedt, Alison L. Atkins, Henrik Hagberg, Marcela Pekna, Carina Mallard (*submitted to Dev. Neurosci. 2010*)
- IV. Detrimental effects of LPS on dividing stem cells in the newborn brain**  
Andrew S. Naylor, Katarina Järlestedt, Justin Dean, Henrik Hagberg and Carina Mallard (*manuscript*)



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