

Central and Systemic Inflammation in Developmental Brain Injury

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ABSTRACT

Brain injury occurring during the perinatal period is an important cause of mortality and morbidity with potentially life long consequences. Both preterm and asphyxiated full term infants are at high risk of developing such injuries, and intrauterine infection has been identified as an independent risk factor. Whilst the primary causes of perinatal brain injury may be diverse and often elude diagnosis, inflammation is a common feature. We have analysed various aspects of inflammation in perinatal models of sterile and infectious insult. Our particular interests have been: initiation of central inflammation, central nervous system (CNS) recruitment of peripheral immune cells, and inflammation-induced disruption of CNS homeostasis and physiological processes.

We demonstrate constitutive expression of all Toll-like receptors (TLRs), a sub-family of pathogen recognition receptors, in the neonatal CNS and active regulation of *TLRs 1, 2, 5, 7 & 8* following, sterile, hypoxic-ischemic (HI) brain injury. We provide evidence of diminished lesion size in TLR2-KO mice, a result strongly implicating TLR2 as an important mediator of lesion development following HI. Additionally, we display active and prolonged recruitment of peripheral immune cells to the injured regions of the CNS following HI, a process that occurs in distinct “waves” and continues for up to two weeks. Interestingly, such recruitment was absent in a model of infectious insult, as initiated by peripheral administration of lipopolysaccharide (LPS). Here, numerous signs of enhanced central inflammation were observed. We detected acute increases in microglial proliferation and total number of microglia, changes coupled to regulation of several inflammation associated genes in the hippocampus. This increased hippocampal inflammatory profile was present for at least two weeks after administration of LPS and occurred in parallel to decreases of neuronal commitment among hippocampal progenitor cells.

Together these results indicate involvement of the TLRs in rapid initiation of inflammation following HI and display active and prolonged participation of peripheral immune cells this inflammatory response. Additionally, we demonstrate that inflammation initiated outside the CNS is sufficient to upregulate cerebral inflammatory responses and transiently disrupt developmental microgliogenesis and neurogenesis.

Keywords: Immune-brain communication, perinatal brain injury, leukocyte migration, TLRs

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AKADEMISK AVHANDLING

som för avläggande av medicine doktorexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligens försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, fredagen den 12 december 2014 kl. 9.00

Av

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Kennedy Krieger Institute, USA**

This thesis is based on the following original studies:

- I. Stridh, L., Smith, P.L., Naylor, A.S., Wang, X. & Mallard, C. Regulation of toll-like receptor 1 and -2 in neonatal mice brains after hypoxia-ischemia. *Journal of neuroinflammation* 8, 45 (2011).
- II. Smith, P.L., Hagberg, H., Naylor, A.S. & Mallard, C. Neonatal Peripheral Immune Challenge Activates Microglia and Inhibits Neurogenesis in the Developing Murine Hippocampus. *Developmental neuroscience* (2014).
- III. Smith, P.L., Hellström Erkenstam, N., Mottahedin, A., Ek, C.J., Hagberg, H. & Mallard, C. Prolonged accumulation of peripheral myeloid cells in a murine model of neonatal hypoxic-ischemic brain injury. *Manuscript*.



UNIVERSITY OF GOTHENBURG

Gothenburg 2014