Inflammation in the immature brain

The role of Toll-like receptors

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, fredagen den 11 november 2011 kl. 9.00

av

Linnea Stridh

Opponent: Dr. Zinaida Wexler
Neonatal Brain Disorders Laboratory
University of California, USA

The thesis is based on the following papers:

I. **Regulation of Toll-like receptor 1 and -2 in neonatal mouse brain after hypoxia-ischemia**
Linnea Stridh, Peter L.P. Smith, Andrew S Naylor, Xiaoyang Wang and Carina Mallard
J. Neuroinflammation 2011, 8:45

II. **Lipopolysaccharide Sensitizes Neonatal Hypoxic-Ischemic Brain Injury in a MyD88-Dependent Manner**
Xiaoyang Wang, Linnea Stridh, Wenli Li, Justin Dean, Anders Elmgren, Liming Gan, Kristina Eriksson, Henrik Hagberg and Carina Mallard
J. Immunol. 2009;183;7471-7477

III. **TLR3 activation increases the vulnerability of the neonatal brain to hypoxia-ischemia**
Linnea Stridh, Xiaoyang Wang and Carina Mallard
In manuscript

IV. **Regulation of Toll like receptors in choroid plexus and endothelial cells in the immature brain after inflammatory stimulation**
Linnea Stridh, Xiaoyang Wang, Holger Nilsson and Carina Mallard
In manuscript

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Linnea Stridh

Department of Physiology, Institute of Neuroscience and Physiology
Sahlgrenska Academy at University of Gothenburg
Göteborg, Sweden

ABSTRACT

Infection/inflammation and/or hypoxia-ischemia (HI) are major causes of perinatal brain injury. Toll-like receptors (TLRs), important components of innate immunity, have been shown to be involved in brain injury, both after infectious and endogenous, non-infectious, stimuli. The **overall aim** of this thesis was to study the expression of TLRs in the immature brain, choroid plexus and endothelial cells after inflammatory stimuli and/or HI, and to investigate the role of TLRs, their adaptor proteins MyD88 and TRIF in brain damaging processes after HI.

TLR stimuli, HI or a combination of them both was performed on mice at postnatal day 9. Brain injury and inflammatory responses were evaluated with immunohistochemistry, RT-qPCR and cytokine analyses.

All investigated TLRs were expressed under basal conditions in the neonatal brain and several of the receptors were regulated in the brain, choroid plexus and blood brain barrier after inflammatory stimuli and/or HI. Additionally, systemic stimulation of TLR 1/2 and TLR 4 decreased the expression of occludin, a tight junction protein, in the choroid plexus. TLR 2 was constitutively expressed in astrocytes in white matter and in neurons in the paraventricular nucleus and contributed to brain damage following HI. In contrast, MyD88 and TRIF did not appear to play a role in the injury process after HI alone. Both lipopolysaccharide (LPS), a TLR 4 ligand, and Poly I:C, a TLR 3 ligand, sensitized the brain to HI in wild type mice. This effect was blocked in MyD88 and TRIF deficient mice. Both Poly I:C and LPS increased the pro-inflammatory cytokine levels in the brain and this increase was blocked/reduced in the TRIF and MyD88 deficient animals.

To conclude, TLRs are expressed under basal conditions and regulated during inflammation in the brain as well as in choroid plexus and blood brain barrier. In particular, we found that TLR 2 contributes to injury following HI, indicating that it has a function in sterile inflammation in the neonatal brain. Further, both MyD88 and TRIF play essential roles in LPS/Poly I:C-sensitized HI neonatal brain injury. These findings suggest that TLRs are important in both physiological and pathological processes in the immature brain and may provide novel targets for neuroprotective therapies in the future.

Keywords: hypoxia-ischemia, immature brain, inflammation, innate immunity, Toll-like receptors

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