Inflammation and neuroprotective strategies in the immature brain after hypoxic-ischemic brain injury

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av

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Avhandlingen baseras på följande delarbeten:

I. Wang X, **Svedin P**, Nie C, Lapatto R, Zhu C, Gustavsson M, Sandberg M, Karlsson JO, Romero R, Hagberg H, Mallard C, **N-acetylcysteine reduces lipopolysaccharide-sensitized hypoxic-ischemic brain injury.** Ann Neurol. 2007 61(3):263-71.

II. **Svedin P**, Guan J, Mathai S, Zhang R, Wang X, Hagberg H, Mallard C, **Delayed peripheral administration of a GPE analogue induces astrogliosis and angiogenesis and reduces inflammation and brain injury following hypoxia-ischemia in the neonatal rat.** Dev Neurosci. 2007; 29: 393-402

III. **Svedin P**, Hagberg H, Sävman K, Zhu C, Mallard C, **Matrix metalloproteinase-9 gene knock-out protects the immature brain after cerebral hypoxia-ischemia.** J Neurosci. 2007 14;27(7):1511-8.

IV. **Svedin P**, Hagberg H, Mallard C, **Neuroprotective effects of matrix metalloproteinase-12 in the developing brain after hypoxia-ischemia.** In manuscript.

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ABSTRACT

Perinatal brain injury, as a result of hypoxia-ischemia (HI) or infection/HI, is a major cause of acute mortality and neurological morbidity in infants and children. The mechanisms of perinatal HI are not fully understood, which makes it difficult to find effective treatment. The aim of the thesis was to investigate the mechanisms of perinatal HI brain injury, and to evaluate different neuroprotective strategies; 1) effects of N-acetylcysteine and melatonin after LPS-sensitized HI, 2) effects of a GPE analogue (G-2mPE) after HI, 3) the involvement of matrix metalloproteinase (MMP) -9 and -12 after HI. An animal model of perinatal brain injury was used in the neonatal rat/mouse, i.e. permanent ligation of the left carotid artery, followed by exposure to a gas mixture with low oxygen content, either alone (HI) or in a combination with infection (LPS/HI). Neuroprotective effects of N-acetylcysteine and melatonin were investigated in neonatal pups after LPS/HI. The drugs were given in multiple doses and brain injury was evaluated 7 days after the HI insult. The neuroprotective effect of post HI administered G-2mPE was investigated in neonatal rats. MMP-9 gene deficient mice were used to evaluate the importance of MMP-9 after perinatal HI. MMP-12 expression after HI was investigated in wild type animals after perinatal brain injury. Marked neuroprotection was found with NAC treatment, which was associated with reduced isoprostane activation and nitrotyrosine formation, increased levels of the antioxidants glutathione and thioredoxin-2 and inhibition of caspase-3, calpain, and caspase-1 activation. A moderate reduction of brain damage was obtained after pre/post treatment with melatonin. Post-HI treatment with G-2mPE attenuated neuronal injury and promoted astrogliosis, as well as blood vessel growth. MMP-9 was shown to play an important role in the development of HI injury in the immature brain, particularly with regard to blood-brain barrier leakage and inflammation. MMP-12 may also be important for the development of brain injury, as the MMP-12 mRNA expression is up-regulated 24 hours after HI and an increased number of cells express MMP-12 in the damaged ipsilateral hemisphere.

Key words: Hypoxia-ischemia, LPS, immature, brain, inflammation, NAC, melatonin, G-2mPE, MMP-9, MMP-12

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