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OSTEOPOTIN IS NEUROPROTECTIVE AFTER NEONATAL HYPOXIC-ISCHEMIC (HI) BRAIN INJURY

F. van Bel

Neonatology, University Hospital Utrecht, Utrecht, The Netherlands

Background: Treatment options of birth asphyxia (BA) are still very scarce. Stimulation of growth factor after neonatal brain damage may reduce BA-related brain damage.

Objective: To identify molecules that contribute to BA-induced brain damage and repair. With PCR array analysis, osteopontin (OPN) was identified as the most important upregulated factor early after BA. We also determined the contribution of endogenous OPN in neonatal HI brain damage and repair.

Design and methods: Nine-day old WT mice were exposed to HI brain damage. Growth factor-related gene expression profiles were analyzed at 1 to 7 days after HI by RT-PCR arrays. To determine the contribution of OPN to brain damage, we used p9 OPN $^{-/-}$ and WT mice. Brain damage, sensorimotor function, cerebral cell proliferation and differentiation were analyzed.

Results: We found that gene expression profiling of 150 genes related to growth factors and neurotrophins showed that expression of 52 genes changed during the first 7 days after HI. OPN was the gene with the most pronounced increase expression at all time points.

We show that in response to neonatal HI, OPN-deficient mice developed increased grey and white matter loss and more pronounced sensorimotor deficits as compared to WT littermates. Furthermore, OPN-deficiency decreases HI-induced cerebral cellproliferation/survival and oligodendrogenesis without affecting neuronal differentiation.

Conclusions: OPN expression is upregulated after HI brain damage and contributes to activation of endogenous repair mechanisms by regulating neuronal proliferation/survival and especially oligodendrocyte diffentiation. The observed promyelinative effect of OPN may offer novel possibilities for therapy targeting white matter injury.