Abstract Sixth Hershey Conference on Developmental Brain Injury

"NF-κB inhibition after neonatal cerebral hypoxia-ischemia: switching transcription factor use preserves cytokine production"

Cora H. Nijboer[1,2], Annemieke Kavelaars[1], Floris Groenendaal[2], Frank van Bel[2], Cobi J. Heijnen[1]

[1]Laboratory of Psychoneuroimmunology and [2]Department of Neonatology, University Medical Center Utrecht, Lundlaan 6, 3584 EA Utrecht, The Netherlands.

"Nijboer, C." <C.Nijboer@umcutrecht.nl>

Objectives: NF-κB is an important transcription factor involved in regulating inflammation and apoptosis. We recently found that NF-κB inhibition by intraperitoneal administration of the NF-κB inhibitor TAT-NBD strongly reduced HI brain damage in a rat model of neonatal hypoxia-ischemia (HI). Surprisingly, NF-κB inhibition and neuroprotection were not associated with inhibition of cytokine production in the brain. In this study, we investigated whether interaction between the NF-κB and JNK/AP-1 pathway can contribute to the regulation of HI-induced cytokine production. Finally, we suggest that early cytokines may constitute a protective mechanism in neonatal HI cerebral damage.

Methods:P7 Wistar rat pups underwent HI by unilateral carotid artery occlusion and hypoxia. Rat pups were treated with the NF-κB inhibitor TAT-NBD, the JNK inhibitor TAT-JBD or both at 0 and 3h post-HI. NF-κB and AP-1 activity, XIAP expression, TNF-α and receptor mRNA expression and cerebral damage were determined.

Results: NF-κB inhibition by TAT-NBD treatment after neonatal HI reduced cerebral damage but did not inhibit TNF-α production. The HI-induced reduction in XIAP, a NF-κB target-gene that is known to negatively regulate the JNK pathway, was more pronounced after TAT-NBD treatment. In addition, cerebral JNK/AP-1 activation was increased after TAT-NBD.

TNF-α production was completely abrogated after inhibition of both NF-κB and JNK/AP-1 by combined treatment with TAT-NBD and TAT-JBD.

TAT-JBD treatment after HI offered significant neuroprotection but to a smaller extent than NF-κB inhibition by TAT-NBD. However, combined treatment with TAT-NBD and TAT-JBD significantly reduced the neuroprotective effect observed after treatment with TAT-NBD alone.

HI-induced expression of death receptor TNF-R1 was reduced and HI-induced expression of protective receptor TNF-R2 was increased when NF-κB activity was inhibited by TAT-NBD.

Conclusions: When NF-κB is inhibited after neonatal HI, switching to use of the JNK/AP-1 pathway, possibly via XIAP, is responsible for preserving early cytokine expression. As abrogation of cytokine production by combined inhibition of the NF-κB and JNK pathways provided less neuroprotection than inhibiting NF-κB alone, we hypothesize that early cytokine production is not detrimental to HI brain injury. We suggest that early TNF-α expression might contribute to neuroprotective effects of TAT-NBD by signalling via TNF-R2.