

Effect of systemic administration of GCSF/SCF or FL on hypoxic/hyperoxic ischemic brain injury in newborn mice

Karina Wegleiter¹, Elke Griesmaier¹, Vera Neubauer¹, Gerald Schlager¹, Martina Urbanek¹, Georg Simbruner¹, Matthias Keller¹

¹Department of Pediatrics IV, Neonatology, Neuropediatrics and metabolic diseases, Medical University Innsbruck, Austria

Background: Hypoxic ischemic (HI) injury is a major cause in the pathogenesis of periventricular leukomalacia in preterm infants, resulting in cognitive deficits and motor disabilities. We have recently shown that the administration of granulocyte colony stimulating factor (G-CSF) and stem cell factor (SCF) increases excitotoxic brain injury in newborn mice, when administered in the acute phase of the insult. When administered after the acute phase of injury, GCSF/SCF significantly reduces excitotoxic injury. However our results obtained in the excitotoxic brain injury model are controversial to published results obtained in different animal models.

Aim: The aim of this study was to evaluate the effect of the haematopoietic growth factors (GCSF/SCF and Fms like tyrosine kinase 3 ligand (FL)) in a neonatal model of hypoxic/hyperoxic ischemic (HHI) brain injury.

Methods: Unilateral carotid artery ligation was performed in neonatal mice on postnatal day 5 (P5) followed by hypoxia (8% O₂) for 15 minutes alternating with hyperoxia (100% O₂) for 10 min, totally 65 min. 60 hours later i) GCSF/SCF (GCSF 200µg/kg, SCF 50µg/kg), ii) FL (100µg/kg) or iii) vehicle was randomly injected intraperitoneally (i.p.) repetitively every 24 hours, 3 or 5 times and endpoints were set at P10, P21 and P120. At endpoints we determined lesion size and analysed rotarod test (functional outcome), open field test (activity and emotionality) and object recognition test (spatial memory) in P120.

Results: HHI resulted in a moderate to severe brain injury with white matter cysts and cortical atrophy. Although there were animals which seemed to benefit (in terms of lesion size and outcome) from these treatments, this did not reach statistical significance (n=10-15).

Conclusion: In the excitotoxic brain injury model the same treatment regimen reduced brain damage. This and the results of this study leads us to speculate that the effect of these treatments strongly depends on the severity of brain injury. In severe brain damage with great tissue loss, the "matrix" (e.g. cells secreting chemoattractants) required for neuroregeneration might be lost.