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G-CSF PREVENTS LONG-TERM BEHAVIORAL DEFICITS AND BRAIN INJURY FOLLOWING NEONATAL HYPOXIA-ISCHEMIA IN RATS

M. Griva[1], G. Kokaraki[1], T. Georgiou[1], F. Karalis[1], C. Simeonidou[1], N. Grigoriadis[2], V. Soubasi[3], E. Spandou[1]

[1]Physiology, [2]Neurology, [3]Neonatology, Aristotle University of Thessaloniki, Thessaloníki, Greece

Background and aims: Granulocyte-colony stimulating factor (G-CSF) has been shown to exert neuroprotective effects in several in vivo models of brain injury mediated by its anti-apoptotic, anti-inflammatory, neurotrophic and excitoprotective action. However, the effect of G-CSF on functional abilities following neonatal hypoxia-ischemia (HI) is still uncertain. The aim of this study was to evaluate the effect of G-CSF on HI-induced long-term behavioral impairment (motor and memory ability) and brain injury.

Methods: Seven-day-old rats underwent unilateral, permanent carotid artery ligation followed by 1h of hypoxia and were divided into 3 groups: A (n=7, sham-operated), B (n=14, HI), and C (n=14, HI-GCSF), post-treated with G-CSF (50 μg/kg). Behavioral tests were performed from days P50-P65, during which motor activity (rota-rod) and learning/memory function (water maze) were examined. Histological analysis was performed at the level of dorsal hippocampus according to a semiquantitative 5-point scale.

Results: HI resulted in significant motor function (102.5±14.8sec) and spatial reference (37.4±5.5sec) and working memory impairment (30.8±4sec) compared to sham-operated rats (rota-rod:213±22sec, reference:14.7±1.8 and working memory:14.2±2sec) ($p< 0.05$). G-CSF-treated rats exhibited significantly improved performance in rota-rod (167.7±14.8sec) and water maze (reference:11.7±1.3 and working memory:17.3±5.5sec) tests, almost reaching the performance of sham-operated animals. Neonatal HI resulted in extensive neuronal damage that was limited after G-CSF administration ($p< 0.05$).

Conclusions: G-CSF administration exerts long-term neuroprotective effect by reducing the HI-induced neuronal injury and neurological deficits. Longer-latency effects implicated in neuroprotective role of G-CSF, such as neurogenesis or neurotrophic action, should be investigated.

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THE APOPTOTIC EFFECT OF PROPOFOL IN IMMATURE RAT BRAIN AND POSSIBLE NEUROPROTECTION BY ERYTHROPOIETIN

C. Pantazis, I. Bendix, R. Herrmann, T. Karen, G. Schlager, M. Keller, U. Felderhoff-Mueser

Neonatology, University of Essen, Essen, Germany

Background: Propofol is a frequently used drug in pediatric anesthesia and neonatology. We have recently shown that exposure of rodent pups by propofol induces neuronal apoptosis in short term.

Aim: The aim of the current investigation is to evaluate

a) mechanisms of propofol induced neurotoxicity and

b) whether the neurotoxic effect can be reduced by Erythropoietin

Methods: Newborn rats were randomized into following groups i) sham ii) Propofol iii) Propofol with Erythropoietin intraperitoneal injections. Animals were killed after 6, 12, and 24 hours and the brains were harvested for gene (Affymetrix Chip) and protein expression (Western Blot) analyses.

Results: Propofol induces caspase-3 activation which was inhibited by systemic treatment with EPO at 12 hours. Primary results of gene expression array analyses indicate that systemic Propofol administration induces a reduction in genes involved in Ca2+-regulatory mechanism as well as phosphoinositide-3-kinase signaling. In western blots analyses Propofol induced a transient activation of pAkt , which was increased by co-administration of EPO. In addition Propofol administration decraesed cytokine IL-18 brain levels. .

Conclusion: Administration of Propofol does not only induces neuronal cell death but also induces major modification in cellular signalling in the developing brain .Cell death induced by Propofol is reduced by co-administration of EPO. Additional investigations analysing the effect of propofol on long-term behavioural outcome and mechanisms of action are mandatory and ongoing.