Neonatal hypoxic-ischemic brain damage: a role for the GRK and β-arrestin machinery

*Kavelaars A*, Lombardi MS, Van den Tweel E, Groenendaal F, Van Bel F, Heijnen CJ
Lab for Psychoneuroimmunology and Department of Neonatology, Division Perinatology and Gynaecology
UMC Utrecht, Utrecht

Background: Neurotransmitters, neuropeptides, and chemokines molecules signal through G protein-coupled receptors (GPCR). GPCR kinases (GRK) and β-arrestins regulate the responsiveness of GPCR. Reduced expression of GRK and β-arrestins leads to supersensitisation of GPCR and increases the response to GPCR ligands.
Aim: To investigate whether neonatal cerebral hypoxic-ischemic (HI) brain damage is associated with changes in the GRK/arrestin machinery.
Methods: Rat pups (p12) were exposed to 90 min hypoxia (FiO2 0.08) after ligation of the right carotid artery, a procedure that induces damage in the ipsilateral hemisphere. At 6- 48 h post HI GRK and β-arrestin protein and mRNA expression were analysed in the ipsi- and contralateral hemisphere.
Results: HI downregulates GRK2 protein but not mRNA expression in both hemispheres at 24-48 h post HI, with a more pronounced effect in the ipsilateral hemisphere. GRK2 is markedly decreased in the hippocampal region of the ipsilateral hemisphere that is known to be severely damaged by HI. In contrast, HI increases β-arrestin1 protein and mRNA levels at 6-12 h post-HI.
Conclusions: Neonatal HI-induced brain damage is associated with specific changes in the GPCR desensitization machinery. We hypothesize that these changes result in supersensitization of multiple GPCR and may therefore contribute to HI-induced brain damage.

Dr. Annemieke Kavelaars, Lab For Psychoneuroimmunology, UMC Utrecht, HP KC03.068.0, Lundlaan 6, 2584 EA Utrecht, t 030-2504360, e-mail a.kavelaars@azu.nl

Speaker in symposium inflammatory responses

session 27