Zusammenfassung

Hypoxic-ischemic encephalopathy (HIE) is a medical condition characterized by evidence of acute or sub-acute brain injury related to a perinatal hypoxic-ischemic (HI) event in the neonate. HIE is a major cause of perinatal mortality and cerebral palsy worldwide. Perinatal HI causes acute injury in the affected brain area and subsequent damage in more remote brain regions, thereby influencing on brain development and long-term brain function.

In a neonatal rat model, we aim here to

i)   study the aryl hydrocarbon receptor (AHR)-signalling pathway which is robustly expressed during early brain development thereby serving as a potential target for modulation of brain injury

ii)  address the question why HIE affects brains in male babies more severely than in female babies

iii) assess the influence of a perinatal HI event on the inherent aging process of the brain studying so-called epigenetic clock genes.

For our study, we will utilize the classical Rice-Vannucci HI rat model (Rice et al., 1981) which consists of left-side common carotid artery ligation with for three hours, for some animals followed by 5 hours hyperthermia. A sham operated group serves as control. Organs will be preserved 24 hours after HI at -80°C: ipsilateral hippocampus, cortex, thalamus; contralateral hippocampus, cortex, thalamus; heart, lungs, gut, liver, kidneys; plasma. The animal experiments will be performed as part of a collaboration with the Experimental Neonatology Group at Bonn University.

Our study group provides particular expertise in studying the role of DNA methylation during early (human) development. We will conduct RNA and DNA isolation; measurement of gene expression of AHR pathways genes and other relevant genes (inflammation, hypoxia) by qPCR; and DNA methylation analysis of AHR pathway genes and epigenetic clock genes (ribosomal DNA) by pyrosequencing.

We hypothesize that AHR serves as a regulator of neurogenesis and neuroinflammation following HI. We expect to get a deepened insight in AHR signalling in the brain in a sex-specific manner. This is important as AHR signalling might serve as a target for pharmacological modulation. Finally, studying DNA methylation and analysis of the epigenetic clock will deepen our understanding whether early HI influences cellular aging in the brain.