PATHOPHYSIOLOGY OF INTRAUTERINE ASPHYXIA

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ABSTRACT:

Background: The premature infant is at increased risk of cerebral white matter damage, often referred to as periventricular leucomalacia, PVL, which is associated with later development of cerebral palsy and cognitive impairment. The etiology of PVL remains unclear, but ischemia-reperfusion followed by generation of free radicals and intrauterine infections have been suggested to play an important role. There still is no effective treatment for PVL.

Aims: The aims of the thesis were to evaluate the fetal electrocardographic (ECG) response to umbilical cord occlusion in the preterm fetal sheep. We also wanted to evaluate the neuropathological outcome following asphyxia and endotoxemia and examine the formation of free radicals, in association with white matter damage, in the preterm fetal sheep brain. Finally, we wanted to investigate possible protective and anti-inflammatory effects of melatonin in the immature brain.

Methods: Fetal sheep at midgestation were subjected to asphyxia by umbilical cord occlusion or endotoxemia by administration of bacterial endotoxin (lipopolysaccharide, LPS). Fetal-ECG, arterial blood pressure and heart rate were recorded. Microdialysis samples from the cerebral white matter were collected and analysed for ascorbyl radicals and the neuroprotective and anti-inflammatory effects of melatonin were examined.

Results: Umbilical cord occlusion resulted in immediate bradycardia, initial hypertension and increase in the T/QRS ratio followed by hypotension and normalisation of the T/QRS ratio and in some cases development of negative T waves. Animals subjected to asphyxia demonstrated activation of microglia cells, axonal injury and loss of oligodendrocytes and astrocytes in the white matter, as well as neuronal loss in subcortical grey matter regions. There was a prolonged and marked increase in ascorbyl radical formation in the brain following intrauterine asphyxia. Endotoxemia resulted in selective white matter damage. In animals treated with melatonin, there was a reduction in the number of activated microglia cells and cell death in the white matter of the brain.

Conclusions: These studies show that the midgestation fetal sheep has the capacity to react with a significant increase in the T/QRS ratio following intrauterine asphyxia. Asphyxia resulted in lesions in both white and subcortical grey matter, whereas endotoxemia resulted in selective white matter damage. During reperfusion, a prolonged and marked increase in free radical production was seen following asphyxia. Treatment with melatonin reduced inflammation and cell death in the cerebral white matter.