PATHOPHYSIOLOGY OF FETAL ASPHYXIA: FACTORS THAT INFLUENCE THE SEVERITY AND DISTRIBUTION OF NEURONAL DAMAGE

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ABSTRACT

Perinatal asphyxia is thought to be a major cause of subsequent neurological deficits. Pathological studies suggest that many of these events occur before birth. However, the relationship between specific prenatal events and neurological outcome is not clear. This thesis tested the hypothesis that certain fetal factors play a role in determining the severity and distribution of neuronal loss following in utero asphyxia.

Chronically instrumented fetal sheep at three different gestational ages; midgestation (90d), late-gestation (120-130d) or near term (>135d) were subjected to either a single or repeated insult. The insult consisted of an episode of either systemic asphyxia (umbilical cord occlusion) or cerebral ischaemia (carotid artery occlusion). The fetal parietal cortical electroencephalogram (EEG), cortical impedance (CI) indicating intracellular edema, blood pressure (MAP), electrocardiogram (ECG) and frequent fetal blood gases and metabolites were measured. Three days after the insult, histopathological analysis or immunohistochemistry was performed to determine neuronal loss and specific neurotransmitters respectively.

Transient (10min) occlusion of the umbilical cord in late-gestation fetuses, resulted in severe fetal asphyxia, hypotension (24 ± 5mmHg, $p<0.01$), bradycardia (72 ± 14bpm, $p<0.001$), depressed EEG activity (-17 ± 2dB, $p<0.001$) and intracellular edema. The intracellular edema resolved within 27 ± 6min, whereas the EEG activity was depressed for 5 ± 2h, despite rapid recovery of pO_2. Neither seizures or infarction were observed. The degree of hypotension, increase in CI, lactate and recovery of post-asphyxial EEG intensity were more marked in 135d fetuses compared with the midgestation fetus ($p<0.01$). Neuronal loss, which was only observed in the older group, was predominantly in the hippocampus and associated with the severity of hypotension during occlusion.

Repeated episodes of cerebral ischaemia, altered the distribution of neuronal loss compared with single insults, inducing damage mainly in the striatum. The frequency of the insults determined the severity of the damage. Similarly, recurrent episodes of fetal asphyxia induced predominantly striatal neuronal loss. Each occlusion resulted in fetal hypoxia and bradycardia accompanied by increased T/QRS ratio as noted on the ECG. Progressively severe hypotension and lactic acidosis developed during successive occlusions. The EEG was depressed and CI increased with each occlusion. After the asphyxial episodes, blood pressure and heart rate returned to normal, while the T wave was inverted for 310 ± 60min. The EEG remained depressed for 90 ± 10min and intermittent seizures developed at 3.3 ± 0.6h after the last occlusion. The extent of neuronal loss correlated with the degree of hypotension, increase in T/QRS ratio, duration of post-asphyxial EEG depression and number of seizures. Immunohistochemical analysis showed loss of striatal GABAergic projection neurons.

These findings demonstrate that certain prenatal factors, such as neurological maturation, pattern of the insult and cardiovascular instability can influence neuronal outcome following fetal asphyxia. An isolated brief episode of asphyxia can lead to selective hippocampal neuronal loss, while repeated insults induce predominantly striatal damage. These distributions of neuronal loss may be associated with postnatal sequelae such as learning disorders and cerebral palsy.

PUBLICATIONS ARISING FROM THIS THESIS

PAPERS:

Mallard EC, Gunn AJ, Williams CE, Johnston BM, Gluckman PD (1992) Transient umbilical cord occlusion causes hippocampal damage in the fetal sheep. *Am J Obstet Gynecol* 167:1423-1430.

Mallard EC, Williams CE, Gunn AJ, Gunning MI, Gluckman PD (1993) Frequent episodes of brief ischaemia sensitise the fetal sheep brain to neuronal loss and induce striatal injury. *Pediatr Res* 33:61-65.

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REVIEWS/CHAPTERS:

Williams C, Mallard C, Tan W, Gluckman P (1993) Pathophysiology of perinatal asphyxia. *Clin Perinatol* 20:305-325.

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ABBREVIATIONS

AMPA:	α-amino-3-hydroxy-5-methyl-4-isoxozolepropionate
ATP:	Adenosine triphosphate
CaO_2:	Oxygen content
CI:	Cortical impedance
CNS:	Central nervous system
D:	Day
dB:	Decibel
EAA:	Excitatory amino acids
ECG:	Electrocardiogram
EEG:	Electroencephalogram
EMG:	Electromyogram
GABA:	γ-amino butyric acid
GAD:	Glutamic acid decarboxylase
GM1:	Monosialoganglioside
H:	Hour
Hb:	Haemoglobin
HR:	Heart rate
Hz:	Hertz
IUGR:	Intrauterine growth retardation
Min:	Minute
MK801:	(+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclo-hepten-5,10-iminemaleate
NMDA:	N-methyl d-aspartate
NO:	Nitric oxide
NOS:	Nitric oxide synthase
PBS:	Phosphate buffered saline
PND:	Postnatal day
pCO_2:	Partial pressure of carbon dioxide
pO_2:	Partial pressure of oxygen
PVL:	Periventricular leukomalacia
S.E.M.:	Standard error of the mean