Introduction

- Maternal intrauterine infection/inflammation is one of the major causes for cerebral palsy (CP).
- Previous studies have demonstrated that increased tryptophan metabolism by the kynurenine pathway occurs with intrauterine infection, and in animal models of neuroinflammation. We have previously demonstrated that this leads to decreased serotonin production in the neonatal brain.

Serotonin staining

Hypothesis

Our hypothesis is that intrauterine inflammation results in:
- Decreased serotonin formation in the fetal and neonatal brain.
- Upregulation of microglia in the fetal brain,
- Inhibiton of kynurenine metabolism following maternal intrauterine inflammation is protective against fetal brain injury.

Materials & Methods

Pregnant rabbits @ G29 in 2 groups

Control no intervention

Control

Somatosensory Cortex

Endotoxin

Maternal inflammation is associated with decreased serotonin concentrations in the brain and decreased serotonin staining fibers in the somatosensory cortex of the newborn rabbit brain.

Tryptophan and kynurenine metabolites in the brain were measured by HPLC. Brain tissue was stained for microglia using Iba-1 and CD11b and compared between endotoxin and control kits. IDO, KMO and KAT levels in the brain were compared between the two groups using PCR.

Results

G29 Control Endotoxin

Serotonin levels

Somatosensory Cortex

Postnatal Day 1 (PND1)

The microglia cells are activated with round cell bodies.

Increased CD11b expressing microglial (red, shammy stain) were seen in brain region in fetal (G29) rabbit brain.

Rabbits subjected to maternal infection/inflammation showed significantly elevated levels of kynurenine in the PVR of G29 fetal brains. Increased formation of kynurenine acid was also noted in the placenta and PVR of fetuses exposed to endotoxin. Although SHAA levels were slightly decreased in the PVR of endotoxin fetuses, it did not reach significance, however a significant decrease in 5HT was seen by PND1 as previously reported by us.

Conclusions

- Maternal intrauterine infection/inflammation results in increased activation of the kynurenine pathway in the fetal and newborn brain.
- This is associated with microglial activation in the brain that activates kynurenine pathway enzymes in the presence of inflammation.
- The kynurenine pathway may be a potent therapeutic target for suppression of toxic kynurenine metabolites and for restoring serotonin levels that is crucial for the normal development of the somatosensory cortex.
- Inhibiting IDO specifically in activated microglia may prevent ongoing injury by increased formation of the downstream excitotoxic kynurenine metabolites

This work is funded by RO1HD090956 (SK) and T32 grant (NW).