Inhibition of the Kynurenine Pathway Leads to Improvements in Neurobehavioral Scores in Maternal Intrauterine Inflammation

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Introduction and Background
• Neurodevelopmental disorders such as cerebral palsy may be induced by alterations in tryptophan metabolism triggered by maternal and fetal inflammation...
• We have previously demonstrated that increased tryptophan metabolism via the kynurenine pathway occurs with intrauterine infection, which leads to decreased serotonin production in the neonatal brain.
• Kynurenine formed by the catalysis of tryptophan by Indoleamine 2,3-dioxygenase (IDO) is metabolized to KYNA by kynurenine amino transferase (KAT) and/or 3-HK, and quinolinic acid by KMO.
• IDO and KMO are induced by interferon gamma and pro-inflammatory cytokines and are upregulated in the placenta in intrauterine infections.
• The metabolites of the KMO pathway are neurotoxic and are associated with oxidative stress and excitotoxicity.
• Our hypothesis is that by targeting the KMO pathway in maternal dams, we will attenuate neuroinflammation and improve motor defects.

Materials and Methods
Pregnant rabbits in the control saline and endotoxin groups underwent laparotomy at gestational day 28 (term pregnancy 35-32 days) and were injected with 1ml of saline or 1ml saline containing 250ug of E.coli endotoxin along the uterine wall. A control group received no surgery. Approximately 4 hours after the insult, the dams were treated with vehicle (saline = 5% DMSO), or KMO-inhibitor (25mg/kg) in vehicle.

Vehicle/Control Treatment
• LPS injection @ G28 and post treatment with vehicle or KMOi

Endotoxin (CP) kits [Exhibit CP phenotype with spastic hind limbs and demonstrated significant impairment in posture, righting reflex, locomotion, and feeding]
• Dams delivered kits on gestational day 31, and kits were randomly assigned numbers.
• After scoring behavior, the kits were sacrificed and brains were collected for RT-PCR and IHC.

Materials and Methods

Results

KMO-inhibitor treatment improves muscle tone and posture scores

KMO-inhibitor treatment improves motor function and birth weight

Conclusions and Future Direction
• Our results indicate that in utero endotoxin exposure leads to increased tone and spasticity, decreased ability to perform complex motor tasks, and that treatment with a KMO-inhibitor improves these scores.
• We also found that treatment decreases the on-going elevation of IFN-γ and IDO.
• The kynurenine pathway may be a potent therapeutic target for suppression of toxic metabolites and for restoring serotonin levels that is crucial for the normal development of the fetal brain.
• Our data indicate that maternal inhibition of the kynurenine pathway may improve spasticity, ability to perform complex motor tasks, and help prevent fetal inflammation by decreasing formation of neurotoxic kynurenine metabolites.
• Future studies will focus on determining appropriate therapies for the mother and/or neonate. While targeting KMO may be more effective for maternal therapy, inhibiting IDO may be more effective in the postnatal period.
• Dendrimer nanoparticle based therapies for targeted inhibition of IDO in activated microglia may help attenuate the injury and restore normal serotonin levels in the newborn brain.

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