[N-69] Inhibition of kynurenine metabolism following maternal intrauterine inflammation is protective against fetal brain injury

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Intrauterine inflammation during pregnancy has been implicated in fetal neuroinflammation and developmental disorders such as cerebral palsy. We hypothesize that maternal and fetal inflammation results in increased tryptophan (TRP) metabolism through the kynurenine (KYN) pathway due to increased expression of the rate limiting enzymes indoleamine2,3 dioxygenase (IDO) and kynurenine mono-oxygenase (KMO) leading to increased formation of the neurotoxic metabolites 3-hydroxykynurenine and quinolinic acid and decreased serotonin (5HT) in the placenta and fetal brain. This is associated with microglial activation along with neuronal loss and oxidative injury in the fetal brain. Maternal treatment with Ro61 8048, a KMO inhibitor will help attenuate the injury.
Pregnant rabbits were administered 20,000 EU of E.coli endotoxin (endotoxin) along the uterus on G28 (term=G31) and were treated intravenously with either 20mg/kg of Ro61 8048 or equal volume of vehicle 4 hours after the laparotomy. A control group received just the vehicle. Placenta and fetal brains were harvested after 24 hours (G29) and analyzed by HPLC for concurrent measurement of all TRP and KYN metabolites, and confirmed by Mass Spectrophotometer. Fetal brains were also evaluated for microglial activation, neuronal loss and oxidative injury. Our results demonstrate that maternal endotoxin exposure results in increased KYN and kynurenic acid (KYNA) with a decrease in 5HT in the periventricular region (PVR) of the fetal brain when compared to controls (n=4 kits /group). Endotoxin kits had significantly increased microglial activation with increased KMO expression in the PVR that mainly co-localized in CD11b staining activated microglia and increased neuronal loss by TUNEL and Floro-Jade staining. There was no difference in TRP levels between the groups. Ro61 8048 treatment led to a 14-fold increase in the fetal brain 5HT/TRP ratio with a 11-fold decrease in the KYN/TRP ratio when compared to the untreated endotoxin group, with KYN levels that were comparable to controls. There was also decreased microglial activation in the fetal brain and neuronal apoptosis when compared to untreated endotoxin kits. In conclusion, this data suggests that maternal inflammation results in increased tryptophan metabolism along the kynurenine pathway that is associated with increased microglial activation and neuronal injury in the fetal brain. Maternal treatment with a KMO inhibitor appears to attenuate this injury.
