Placental Allopregnanolone Loss Alters Fetal Brain Development in a Novel Mouse Model

Background: A major consequence of preterm birth is premature loss of the placenta and the support it provides. The placenta functions as a critical neuroendocrine organ that supplies the developing fetus with essential hormones, including neurosteroids such as allopregnanolone (ALLO). ALLO is a downstream metabolite of progesterone that is produced via a two-step enzymatic conversion process that depends specifically on 3α-hydroxysteroid dehydrogenase (3αHSD; in mouse encoded by the *Akr1c14* gene). ALLO is a potent, positive allosteric modulator of $GABA_A$ receptors. Prenatal ALLO is provided by the placenta and concentrations are especially high in late gestation, when synapses are predominantly GABAergic and GABA is excitatory, rather than inhibitory. This neuronal excitation is critical for maturation and integration of neurons into developing circuits. ALLO is implicated in regulation of neurogenesis, neural outgrowth and survival, migration and synapse stabilization. Thus the consequences of ALLO alterations may persist into adulthood.
Objective: Design and validate a mouse model for loss of placental ALLO, mimicking loss of placental endocrine support with preterm birth, to directly test the importance of placental ALLO for cortical and hippocampal development.
Design/Methods: *Akr1c14* floxed mice designed by our laboratory were bred with CYP19-CRE mice to create a placental specific knockout of *Akr1c14* (Akr1c14cKO). Tissue-specific gene knockout was validated by qPCR and *in situ* hybridization. Supression of ALLO production was confirmed by mass spectroscopy. Immunohistochemistry, gene expression assays and progenitor labeling techniques were used to assess anatomical changes at multiple developmental timepoints. Adult mice were tested on a battery of behavioral tests (open field, Y maze spontaneous alteration, 3-chamber sociability, and novel object recognition).
Results: Efficient and specific placental knockdown of *Akr1c14* was confirmed. Here, we present data on the long-term consequences of placental *Akr1c14* knockdown. Preliminary results suggest that adult Akr1c14cKO mice exhibited higher anxiety, decreased sociability, and impaired cognitive functioning compared to litter-mate controls. The altered cortical lamination seen in embryonic brain appears to persist into adulthood and interneuron deficits (specifically, calretinin and parvalbumin subtypes) are seen.
Conclusion: Our results suggest that loss of placental ALLO can dysregulate early cortical development, including GABAergic signaling, resulting in long-lasting neurological deficits. The behavioral deficits mirror those seen in human preterm survivors. Placental ALLO regulates cortical development and may alter GABAergic interneuron development in key regions, including hippocampus and cortex. Our novel placental knockout model allows for direct testing of the mechanisms involved in this dysfunction and will allow testing of neurological rescue using ALLO and other placental hormones.