Oxytocin Signalling and Subsequent Maternal Care Deficits in a Retinoic Acid Deficiency Model of FASD

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Introduction: Fetal Alcohol Spectrum Disorder (FASD) is the most common neurodevelopmental disorder in children, with a prevalence of 1-5% in Canada. The *Gsc:Cyp26A1* mouse model was designed to biochemically mimic ethanol-induced retinoic acid deficiency at gastrulation. While *Gsc:Cyp26A1* mice phenocopy many traits of FASD, surprisingly, *Gsc:Cyp26A1* mothers also display aberrant maternal care behavior, with very few or no pups surviving past their first day. We hypothesize that retinoic acid deficiency in early development leads to subsequent deficits in Oxytocin (Oxt) signaling and maternal care.

Methods: Oxt expression in the oxytocin producing centres of the brain (the supraoptic and paraventricular nuclei of the hypothalamus) was determined by immunohistochemistry and in-situ hybridization of forebrain sections of pregnant P90 *Gsc:Cyp26A1* and WT pregnant mice using oxytocin-Neurophysin I antibody (N=3) or Oxytocin-Neurophysin I probe (N=1), respectively. Maternal care was assessed by pup survival (n=11 litters) and pup retrieval (n=2 litters) behavioural assays in *Gsc:Cyp26A1*, WT and Tg2.3 (phenotypically WT) mice.

Results: Immunohistochemistry and in-situ hybridization experiments revealed that *Gsc:Cyp26A1* mothers are deficient in Oxytocin-Neurophysin I expression compared to WT mothers. Examination of *Gsc:Cyp26A1* brain sections revealed paraventricular nuclei structural aberrations and other defects in maternal structures in the hypothalamus. All pups of *Gsc:Cyp26A1* dams failed to thrive in the pup survival assay (0% vs 100% for WT and Tg2.3 mothers). *Gsc:Cyp26A1* mothers also failed to complete the pup retrieval test within an established time frame (over 360 s vs 149 and 130 s for WT and Tg2.3 mothers, respectively).

Conclusion: Our data revealed that *Gsc:Cyp26A1* dams are Oxt deficient and have structural aberrations in their forebrain that appear to be of developmental origin. The established Oxt deficiency can explain the poor results of the *Gsc:Cyp26A1* mothers in pup survival and retrieval assays, and suggests the underlying etiology for maternal care deficits in these mice.