

## OR18-2: Cell Fate Decisions in the Developing Hypothalamic Anteroventral Periventricular Nucleus Are Regulated By Canonical Notch Signaling

**Sunday, April 02, 2017**

**11:30 AM - 11:45 AM**

📍 **OCCC - W207**

The hypothalamic anteroventral periventricular nucleus (AVPV) is the major regulator of reproductive function within the hypothalamic-pituitary-gonadal (HPG) axis. Despite an understanding of the function of neuronal subtypes within the AVPV, little is known about the molecular mechanisms regulating their development. Previous work from our lab has demonstrated that Notch signaling is required in progenitor cell maintenance and formation of Kisspeptin neurons of the arcuate nucleus (ARC) while simultaneously restraining POMC neuron number. Based on these findings, we hypothesized that the Notch signaling pathway may act similarly in the AVPV by promoting development of Kisspeptin neurons at the expense of other neuronal subtypes. To address this hypothesis, we utilized a genetic mouse model with a conditional loss of *Rbpj* in *Nkx2.1* expressing cells (*Rbpj* cKO). By means of immunohistochemistry and *in situ* hybridization, our findings have shown that loss of *Rbpj* resulted in a loss of *Hes1* and a selective reduction in *Hes5* expression in the anterior hypothalamic region that gives rise to the AVPV. Morphologically, we noted a dramatic expansion of the tissue of the presumptive AVPV and cellular proliferation, as marked by Ki-67, appeared increased in the hypothalamic ventricular zone (HVZ). We found this to correspond to an increase in general neurogenesis and significantly more TH-positive neurons in *Rbpj* cKO mice at E13.5. Additionally, we noted that conditional loss of Notch resulted in a failure to maintain the HVZ and an increase in OLIG2-positive oligodendrocytes. By 5 weeks of age in female *Rbpj* cKO mice, TH-positive cells were readily detected in the AVPV but few Kisspeptin neurons are present. We next hypothesized that inhibition of Notch signaling in a pure progenitor population would be sufficient to drive TH neuron differentiation. Utilizing an *in vitro* primary hypothalamic neurosphere assay, we demonstrated that treatment with the chemical Notch inhibitor DAPT results in a significant reduction of canonical Notch signaling genes. Reductions in *Hes1*, *Hes5*, and *Hey1* corresponded with an increase in *Olig2* expression and decrease in *Gfap* expression, suggesting a role for Notch signaling in fate decisions between a oligodendrocytic versus glial lineage. After 6 days of DAPT treatment, a modest increase in expression of TH in both the cell soma and neurite extensions was observed, suggesting that inhibition of Notch signaling alone is enough to bias progenitors towards a dopaminergic fate. Taken together, these data further support that Notch is an important fate selector of all Kisspeptin neurons and actively suppresses premature differentiation of other neuronal subtypes in the AVPV similar to the ARC.

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## **Disclosure**

Nothing to Disclose: MJB, KBK, GHU, LTR

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