The Neurodevelopmental Effects of Synthetic Glucocorticoid at Different Time Point on Stress and Metabolism Gene Expression in the Developing Hypothalamus.

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**Abstract/Introduction**

The clinical use of synthetic glucocorticoids (SGCs) in newborns to enhance respiratory function has been shown to have other undesired effects such as increasing the risk of developing metabolic and neuroendocrine disorders in adulthood.

In this study, we tested the hypothesis that exposure to the SGC dexamethasone (DEX) at different time points during early development will alter expression profiles of hypothalamic genes in the adult rat.

Rats were treated with DEX at Postnatal Day (PND) 4-6 and the effects of this exposure on gene expression were compared to that from a previous study in which fetuses were exposed to DEX at gestation day (GD) 18-21 by treatment of pregnant dams.

### Hypothalamic Genes of Metabolism Measured

Thyrotropin releasing hormone (TRH) is a key neuropeptide found in the paraventricular n. (PVN) and is responsible for regulating hypothalamic-pituitary-thyroid (HPT) act function. It ultimately affects T3 and T4 secretion to regulate protein, fat, and carbohydrate metabolism.

- **Ghih** / Somatostatin is also found in neurons in the PVN and it acts upon the pituitary to inhibit GH release.
- **K1** - insulin-like growth factor 1 (IGF-1), plays a role in childhood growth and anabolic effects in adults

### Hypothalamic Genes of Stress Measured

- **Oxt** (OT) - aside from its role in birth and lactation, it decreases sympathetic activity and inhibits the secretion of cortisol. Thereby playing a role in inhibiting the stress axis.

**Methods**

Postnatal DEX treatment alters TRH mRNA levels in PVN

![Image](image1)

**Postnatal DEX treatment does not alter TRH Neuron and fibers numbers**

![Image](image2)

**Postnatal DEX treatment alters oxytocin mRNA levels in PVN**

![Image](image3)

**Postnatal DEX exposure alters Ghih mRNA expression**

**Figure 1**

**Figure 2**

**Figure 3**

**Figure 4**

**Figure 5**

**Figure 6**

**Figure 7**

**Comparison Post DEX vs. Pre DEX**

**Trh**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>PND7</td>
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<tr>
<td>PND9</td>
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<tr>
<td>PND11</td>
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**Ghih**

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<td>PND15</td>
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**Oxt**

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**Conclusion**

- Different critical windows exist for SGC treatment to affect expression of genes in the hypothalamus. *Trh*, *Trh* neurons, *Oxt* levels all seem to be affected differently by DEX treatment at different times.

- Trh expression was decreased in the adult animals when DEX was administered either prenatally or postnatally.

- TRH neuron and fiber density in the PVN showed decreases that were only seen in the offspring treated with DEX prenatally.

- Collectively, these data demonstrate that permanent programming effects of SGCs on hypothalamic gene expression are dependent upon the timing of the exposure (gestational vs post gestational).

**Future Directions**

- One possible mechanism that should be further explored is the role of epigenetic marks on DNA in the persistence of these effects into adulthood.

- Studies measuring methylation of CpG islands in Trh and Oxt promoters regions might help us understand the mode of action. It would also be interesting to see if the changes in gene expression correlate with changes in neuron proliferation or death.

- IHC of neuron population of Oxt in the PVN may show changes in neuron population.

- The exact critical window of each gene should be narrowed. Repeating this experiment with additional exposure points such as GD 21 to birth, and PND 3 to PND 21 could determine the exact critical window of vulnerability for each of the genes measured in this paper.