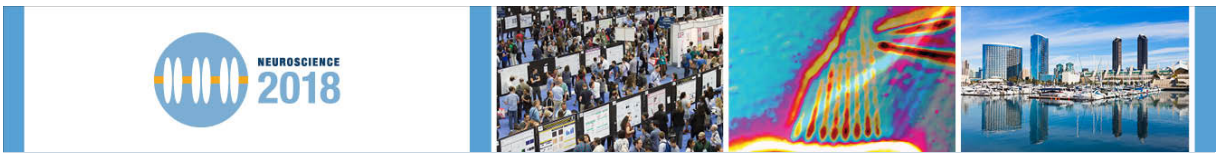

(https://www.abstractsonline.com/pp8/#!/4649)

Session 727 - Angelman and Other Developmental Disorders

Add to Itinerary

727.04 / B23 - Ectopic brain-derived insulin-like growth factor-1 partially rescues neuroanatomical defects associated with developmental hypothyroidism

November 7, 2018, 1:00 PM - 5:00 PM | SDCC Halls B-H

Presenter at Poster
Wed, Nov. 7, 2018, 4:00 PM - 5:00 PM

Grant Support
American Thyroid Association Research Grant

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Disclosures
A. Grond: None. **K.E. Saatman:** None. **D.S. Sharlin:** None.

Abstract
Insufficient thyroid hormone (TH) during development results in permanent neurological deficits. These deficits are the result of neuroanatomical defects that include smaller brain, fewer parvalbumin neurons, and hypomyelination. Interestingly, insufficient insulin-like growth factor 1 (Igf-1) during development results in similar neuroanatomical defects to those reported for developmental hypothyroidism. Thyroid hormone is known to indirectly influence serum Igf-1 levels through its regulation of pituitary growth hormone (GH) secretion which stimulates hepatic Igf-1 production. Our lab and others have observed decreases of local brain-derived Igf-1 in the developing hypothyroid mouse brain. This observation suggests that deficits associated with low TH during development may be the result of altered brain-derived Igf-1. Considering this, we sought to determine whether ectopically expressing Igf-1 in the developing brain could rescue neuroanatomical defects associated with low TH. To accomplish this, the tet-off transgenic system was used where mice harboring the tetracycline transactivator protein driven by the human GFAP promoter (tTA-GFAP) were crossed with mice containing the human Igf-1cDNA under the control the TET response element (Igf1-pTRE) transgene. Double transgenic (dTg) offspring carrying both the tTA-GFAP and Igf1-TRE genes overexpress Igf-1 specifically in brain astrocytes. Timed-pregnant mice were treated with thyroid gland inhibitors from embryonic day 14.5 (E14.5) until postnatal day 14 (P14) to induce a hypothyroid state in pups. At P14, pups were weighed and sacrificed, trunk blood was collected, and brains were dissected, weighed, and immediately frozen. Hippocampal structure, known to be disrupted by developmental hypothyroidism, was assessed by fluorescent imaging using DAPI staining. Our initial results indicate that ectopic expression of Igf-1 in the brain (dTg mice) rescues hypothyroidism-induced reductions in brain weight without increasing body weight. In addition, the ectopic expression of Igf-1 restored hypothyroidism-induced perturbations in dentate gyrus size. Ongoing studies are using quantitative real-time PCR on micro-dissected cortical and hippocampal samples to quantify myelin associated glycoprotein and parvalbumin mRNAs. Taken together, our findings support the idea that ectopic brain-derived Igf-1 rescues neuroanatomical defects caused by hypothyroidism and implicates TH in the regulation of brain Igf-1.

Abstract Citation