Thyroid

HPT-AXIS AND THYROID HORMONE ACTION

Transcriptome Analysis Under Differential Thyroid Hormone Treatment During Mouse Cerebellar Development.

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SAT-441

Background: Thyroid hormone (TH) plays essential roles in the development of the cerebellum by regulating transcription of target genes. TH binds to TH receptor (TR) located in the cell nucleus and stimulates transcription through TH response element (TRE). The expression of many genes is temporary and spatially regulated by TH during cerebellar development. However, the mode of transcription by TR may vary among target genes. In the liver, different duration of TH exposure resulted in distinct gene expression profiles. To examine the mechanisms of transcriptional regulation by TH in cerebellar development, gene expression profile induced by various TH exposure duration was studied. Methods: Anti-thyroid drug propylthiouracil (250 ppm in drinking water) was administered to C57BL/6J mice from the gestational day 14 to postnatal day (P) 7 to generate perinatal hypothyroid mice. To study the effect of continuous TH exposure, TH was subcutaneously administered to hypothyroid pups from P2 to P7 (6 days group). To study the effect of single TH administration, TH was injected on P7 and mice were sacrificed either 6 (6 hours group) or 24 hours (24 hours group) after injection. Cerebellar samples were collected to extract RNA and subject to microarray analysis. Microarray results were confirmed by RT-qPCR. Results: In microarray result, compared with mRNA levels of hypothyroid mice, 6 days group induced upregulation in 1007 genes and downregulation in 1009 genes, 6 hours group induced upregulation in 355 genes and downregulation in 977 genes, and 24 hours group induced upregulation in 365 genes and downregulation in 1121 genes. Only 7.6% of the genes were overlapped in three groups among positively regulated genes. In contrast, 57.2% of the genes were common in the negatively regulated genes. In RT-qPCR result, among genes known to harbor TRE, Hairless, Pcp2, and Nrgn, showed differential upregulation patterns. Hairless was upregulated in all groups, whereas Pcp2 was upregulated only in 5 days group and Nrgn was not upregulated in all groups. These results suggest that different mode of transcriptional regulation occurred in an exposure time-dependent manner of TH. Conclusion: We identified gene groups whose expression were modified by TH during cerebellar development. TH distinctively regulates transcription of target genes depending on the exposure schedule in mouse developing cerebellum.

Adipose Tissue, Appetite, and Obesity

RARE CAUSES AND CONDITIONS OF OBESITY: PRADER WILLI SYNDROME, LIPODYSTROPHY

Livoteotide (AZP-531), an Unacylated Ghrelin Analogue, Improves Hyperphagia and Food-Related Behaviors Both in Obese and Non-Obese People with Prader-Willi Syndrome

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SUN-609

Prader-Willi syndrome (PWS) is a rare, complex neuro-developmental genetic disorder characterized by hyperphagia and abnormal food-related behaviors that contribute to severe morbidity and early mortality and to significant burden on patients and caregivers. While a majority of people with PWS is obese, hyperphagia is observed in both obese and non-obese people with PWS. There is currently no approved treatment for hyperphagia in PWS. People with PWS have increased circulating levels of the orexigenic hormone acylated ghrelin (AG) with a relative deficit of unacylated ghrelin (UAG), a hormone which counteracts many of AG’s effects. Livoteotide (AZP-531) is a first-in-class UAG analogue previously shown to improve hyperphagia, food-related behaviors, and metabolic parameters, and to be well-tolerated in a Phase 2a trial in PWS. [Allas S et al. (2018) PLoS ONE 13(1): e0190849] Here we present additional analyses that examine the effects of livoletide in obese vs non-obese people with hyperphagia in PWS.

Methods: The Phase 2a trial was a randomized, double-blind, placebo-controlled study which included 47 people with PWS. Participants received a daily subcutaneous injection of livoletide (n=23) or placebo (n=24) during a 2-week treatment period. The study population was divided based on the body mass index (BMI) into obese (BMI ≥ 30 kg/m²) and non-obese (BMI < 30 kg/m²) groups. The effect of livoletide on hyperphagia and food-related behaviors was assessed by the change from baseline in the 9-item Hyperphagia Questionnaire (HQ).

Results: There was a total of 34 obese and 13 non-obese subjects in the study. As expected, baseline BMI, body weight (BW) and waist circumference (WC) were significantly higher in obese vs. non-obese PWS subjects (BMI: 42.6 ± 6.0 vs 26.1 ± 2.8, BW: 103.5 ± 23.0 vs 68.5 ± 9.1 and WC: 118.3 ± 15.5 vs 91.8 ± 7.7, respectively, p<0.0001). There was no significant difference with respect to the ratios of males to females or of deletion to non-deletion between the 2 populations. Hyperphagia scores were similar at baseline for obese and non-obese participants (HQ score adjusted for 0 to 36 scale to reflect 9-item HQ-CT: 12.8 ± 7.0 vs 14.0 ± 7.8, p=0.6083, respectively). Fasting AG and UAG levels were lower in the obese vs. non-obese groups (AG: 93.6 ± 72.6 vs 122.1 ± 54.4, p=0.0275; UAG: 123.9 ±
87.2 vs 154.1 ± 62.6, p=0.0219, respectively). Livoletide-treated participants experienced similar improvements in hyperphagia and food-related behaviors as measured by the HQ whether they were obese or non-obese.

**Conclusions:** These results highlight the potential of livoletide for treating hyperphagia in both obese and non-obese people with PWS and hyperphagia. Livoletide is being investigated further in the ZEPHYR Phase 2b/3 trial, an ongoing pivotal study on the long-term safety and efficacy of livoletide in the treatment of hyperphagia and food-related behaviors in people with PWS.

**Thyroid**

**THYROID DISORDERS CASE REPORTS II**

**Sudden Onset of Malabsorption**

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**SAT-509**

Celiac disease (CD) is an immune-mediated enteropathy caused by a reaction to gliadin which responds to a restriction to dietary gluten. It has been traditionally recognized in children and young adults, although, recently, detection in the elderly population has increased. CD occurs in 2–5% of patients with autoimmune hypothyroidism, and is more prevalent in this group than in the general population.

An 82-year-old Caucasian woman with primary hypothyroidism and a BMI of 16 is referred to our endocrinology clinic for help with the management of hypothyroidism. She had a history of well controlled hypothyroidism on weight-dosed levothyroxine for many years until several months prior when she developed sudden onset of diarrhea and weight loss. Since then, her thyroid function tests showed an elevated TSH despite medication adherence. Her levothyroxine dose was steadily increased to 300 mcg daily and yet, her TSH still remained elevated. Laboratory work up was done which revealed elevated transglutaminase antibodies, suggesting the diagnosis of CD. The patient refused an endoscopy for a tissue diagnosis. Even though the patient has been diagnosed with CD, she has trouble following a gluten free diet and still has intermittent diarrhea and high levothyroxine requirements.

Although lack of medication adherence is common, it is important to exclude gastric or intestinal causes of malabsorption in patients with high thyroid replacement requirements. Elderly patients often have paucity of symptoms, so high clinical suspicion is necessary to diagnose these patients.

**Neuroendocrinology and Pituitary**

**ADVANCES IN NEUROENDOCRINOLOGY**

**Role of Activin, Follistatin, and Inhibin in the Regulation of KISS-1 Gene Expression in Hypothalamic Cell Models**

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**SUN-244**

Kisspeptin (encoded by the Kiss-1 gene) in the arcuate nucleus (ARC) of the hypothalamus governs the hypothalamic-pituitary-gonadal (HPG) axis by regulating pulsatile release of gonadotropin-releasing hormone (GnRH). Meanwhile, kisspeptin in the anterolateral