Crem and *Ramp3*. Forskolin treatment displayed no significant variations in OC ring morphology or *Crem* and *Ramp3* mRNA expression between *Gnas+/-m, Gnas+/-p* and WT cultures. Both WT and *Gnas+/-p* OCs displayed appropriate responses to sCT, as indicated by a significant disruption in actin ring morphology and increased *Crem* and *Ramp3* mRNA expression when compared to vehicle-treated controls. SCT-treated *Gnas+/-m* OCs, however, displayed only mild disruptions in actin ring morphology, and we observed significant reductions in *Ramp3* expression compared to WT as well as reductions in *Crem* compared to WT and *Gnas+/-p*. These data suggest evidence of partial calcitonin resistance within *Gnas+/-m* OCs due to impaired $G\alpha_s$- signaling. These data correlate with previous clinical observations of calcitonin resistance in PHP1A patients. Because these findings were observed only within *Gnas+/-m* cultures, future work is warranted to determine whether this impaired receptor activity may be attributed to partial *Gnas* imprinting within OCs or the myeloid lineage.

Pediatric Endocrinology

HOT TOPICS IN PEDIATRIC ENDOCRINOLOGY

Pubertal Onset Occurs in Female Mice Lacking Paternally Expressed Dlk1 Despite Lower Leptin and Kisspeptin Levels

Delanie B. Macedo, MD, PhD[1], Ana Paula Abreu, MD, PhD[2], Melissa Magnuson, BS[1], Han Kyeol Kim, BS[3], Alessandra Mancini, PhD[4], Ana Claudia Latronico, MD, PhD[5], Rona Stephanie Carroll, PhD[2], Ursula B. Kaiser, MD[6].
[1]Brigham and Women's Hospital/Harvard Medical School, Brookline, MA, USA, [2]Brigham and Women's Hospital, Boston, MA, USA, [3]Brigham and Women's Hospital, Brookline, MA, USA, [4]BRIGHAM AND WOMEN'S HOSPITAL, Boston, MA, USA, [5]Sao Paulo Medical School, Sao Paulo University, Sao Paulo, Brazil, [6]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

The timing of puberty in females is highly sensitive to metabolic cues and energy reserves. Epidemiologic studies indicate a relationship between increased body mass index and earlier puberty in girls. In contrast, a significant delay in puberty and menarche is seen in girls who have diminished body fat. Multiple peripheral hormones are responsible for transmitting metabolic information to hypothalamic kisspeptin and GnRH neurons. Sufficient levels of leptin, an adipose tissue hormone with a permissive/stimulatory effect on the metabolic control of reproduction, are required for puberty onset, reproductive function and fertility. Loss-of-function mutations in the *Delta-like homolog 1* (*DLK1*) gene have been described in girls with central precocious puberty (CPP) and increased body fat, suggesting a link between metabolism and reproduction. *DLK1* is a paternally expressed gene located on human chromosome 14q32.2 in a locus associated with Temple syndrome (TS). *Dlk1* knockout mice display pre- and postnatal growth retardation, a phenotype that overlaps with TS. We have shown that *Dlk1* deficient female mice achieved puberty at the same age as wild type mice, despite a considerably lower body weight (BW) ("relative precocious puberty"). To date, the mechanisms of action of *Dlk1* in determining pubertal onset remain unknown. In this study, we used a *Dlk1* deficient mouse model to explore the influence of Dlk1 in the regulation of reproductive axis, particularly its effects on leptin and/or kisspeptin, a major excitatory factor of the reproductive axis. By RT-qPCR and Western blot, we confirmed that both *Dlk1* mRNA and protein were undetectable in the mediobasal hypothalamus (MBH) of $Dlk^{+/p-}$ (which inherited the mutant allele from their father), but it was present in $Dlk^{+/+}$ mice. White adipose tissue (WAT) and blood were collected from $Dlk^{+/p-}$ and $Dlk^{+/+}$ female mice at postnatal day (PND) 26, and MBH tissue was obtained from both groups at PND 15, 26 and 60. Quantification of total WAT showed no significant difference between $Dlk1^{+/p-}$ and $Dlk1^{+/+}$ mice (p=0.8) at PND26, even after correction for total BW (p=0.29). Hypothalamic mRNA levels of *Kiss1* and *Socs3*, a downstream mediator of leptin signaling, were measured by RT-qPCR. *Kiss1* mRNA levels were significantly reduced in the MBH of $Dlk1^{+/p-}$ mice at PND15 and PND60, but no significant difference was found at PND 26. *Socs3* expression was significantly lower in $Dlk1^{+/p-}$ mice (p=0.04) as a result of the reduced circulating levels of leptin (ELISA) observed in these mice at PDN26 (p=0.01). Our findings suggest that the absence of *Dlk1* may attenuate the metabolic effects of low body weight and low leptin levels on puberty onset and that, as seen in humans, DLK1 is an important link between body weight and pubertal development. Finally, Dlk1 deficiency leads to activation of the reproductive axis despite lower levels of kisspeptin.

Pediatric Endocrinology

HOT TOPICS IN PEDIATRIC ENDOCRINOLOGY

Racial/Ethnic Disparities in the Investigation and Treatment of Pediatric Growth Hormone Deficiency

Colin Patrick Hawkes, MD PhD[1], Hareesh Gunturi, MS[1], Andrew Nahum Dauber, MD[2], Joel N. Hirschhorn, MD,PhD[3], Adda Grimberg, MD[4].
[1]The Children's Hospital of Philadelphia, Philadelphia, PA, USA, [2]Children's National Medical Center, Washington, DC, USA, [3]Boston Children's Hospital, Boston, MA, USA, [4]Children's Hospital Philadelphia, Philadelphia, PA, USA.

Introduction: In the United States, non-Hispanic white (NHW) children are disproportionately over-represented relative to children of racial and ethnic minorities in pediatric growth hormone (GH) treatment registries. This study sought to determine if this racial inequity is due to differences in GH stimulation testing and/or GH prescribing patterns in children referred for endocrine evaluation of short stature.
Methods: Retrospective chart review was performed including children aged 2-16 years, with height z-score ≤ -1.5, and of NHW, non-Hispanic black (NHB) or Hispanic race/ethnicity, referred for endocrine growth evaluation between January 1, 2012 and December 31, 2019. Age, sex, anthropometry, GH stimulation test results and GH treatment data were extracted. Comparisons between NHB, NHW and Hispanic children were performed using analysis of variance, chi-squared tests, Mann Whitney U and logistic regression tests.
Results: This study included 7,425 patients (5,905 NHW, 800 NHB, and 720 Hispanic). GH stimulation testing was

performed in 992, and 576 were prescribed GH. NHW children were 1.4 (95% CI 1.04 - 1.8) times more likely than NHB children and 1.7 (95% CI 1.2 - 2.2) times more likely than Hispanic children to undergo GH stimulation testing. NHB children treated with GH had: 1) lower median peak GH concentration when compared with NHW (p=0.02) and Hispanic (p=0.08) children (NHB 4.7 [1.2, 8.3] ng/ml, NHW 7.2 [4.9, 9.7] ng/ml, Hispanic 7.1 [4.3, 11.9] ng/ml); 2) lower median height z-scores than NHW (p=0.01) but not Hispanic children (p=0.5); and 3) a greater height deficit from mid-parental height when compared with NHW (p=0.01) and Hispanic (p=0.002) children

Discussion: Racial and ethnic disparities are present in the evaluation and treatment of children with disordered growth. This likely results from both over-investigation of NHW children as well as under-investigation and under-treatment of children from minority communities. The evaluation and treatment of children with short stature should be determined by clinical concern alone, but this is unfortunately not current practice.

Pediatric Endocrinology

HOT TOPICS IN PEDIATRIC ENDOCRINOLOGY

Topline Results of the CARE-PWS Phase 3 Study: Intranasal Carbetocin Improves Hyperphagia and Anxiety and Distress Symptoms in Prader-Willi Syndrome (PWS)

Davis Ryman, MD PhD[1], Cheri L. Deal, MD, PhD, FRCPC, FAAP[2].

[1]Levo Therapeutics, Skokie, IL, USA, [2]Université de Montréal/ Research Center CHU Sainte-Justine, Montreal, QC, Canada.

Prader-Willi syndrome (PWS) is a complex genetic disorder associated with multiple neuroendocrine abnormalities including significantly decreased hypothalamic oxytocin levels, resulting in symptoms of severe hyperphagia (an unrelenting false sense of starvation) and multiple severe neuropsychiatric and behavioral issues. CARE-PWS, a multi-center, randomized, double-blind, placebo-controlled phase 3 study, has evaluated the efficacy, safety, and tolerability of intranasal carbetocin, a selective oxytocin receptor agonist, in participants with PWS.

Eligible participants aged 7 through 18 with genetically confirmed PWS were randomized in equal proportions to three treatment arms for the 8-week placebo-controlled period of the study: carbetocin 9.6 mg, carbetocin 3.2 mg, or a matching placebo, administered by nasal spray three times a day with meals. The primary endpoint assessed changes from baseline to week 8 in Hyperphagia Questionnaire for Clinical Trials (HQ-CT) or Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) scores for the carbetocin 9.6 mg arm vs placebo, and the first secondary endpoint assessed changes from baseline to week 8 in HQ-CT or CY-BOCS scores for the carbetocin 3.2 mg arm vs placebo. Additional secondary endpoints included changes from baseline to week 8 in PWS Anxiety and Distress Questionnaire (PADQ) scores, and Clinical Global Impression of Change (CGI-C) scores evaluating the overall change in severity of PWS symptoms at week 8.

Due to COVID-19, enrollment was closed early with 119 evaluable participants for the primary analysis. In the carbetocin 9.6 mg arm, trends toward numerically greater improvements in HQ-CT and CGI-C scores relative to placebo were observed but did not reach statistical significance; however, the carbetocin 3.2 mg arm demonstrated a significant improvement in HQ-CT scores (LS mean improvement vs placebo -3.14 points, p=0.016). In the 3.2 mg arm, additional consistent evidence of improvements versus placebo was seen in multiple secondary endpoints, including CGI-C (p=0.027) and PADQ (p=0.027). Numeric trends toward improvement in CY-BOCS scores were observed in each dose arm, but did not reach statistical significance versus placebo. During the subsequent long-term follow-up period of the study, both carbetocin arms have experienced continued numeric improvements from baseline across multiple endpoints. Intranasal carbetocin was generally well-tolerated; the most frequently reported adverse event was flushing, which was generally mild and transient.

In conclusion, results of the CARE-PWS study support that intranasal carbetocin appears to be safe and well tolerated, and reduces hyperphagia and anxiety and distress behaviors in PWS.

Pediatric Endocrinology

PEDIATRIC ENDOCRINOLOGY CASE REPORT

22q13 Duplication in Newborn With Dysmorphic Features: The Role of SOX10 in Disorders of Sex Development

Batoul Hammoud, MD[1], Natalie Marie Hecht Baldauff, DO[2], Svetlana Yatsenko, MD[1], Selma Feldman Witchel, MD[3].

[1]UMPC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA, [2]Children's Hospital of Pittsburgh, Coraopolis, PA, USA, [3]UPMC Children's Hospital of Pittsburgh University of Pittsburgh, Pittsburgh, PA, USA.

Background: The 46,XX testicular disorder of sex development (DSD), also known as 46,XX male reversal, is a rare form of DSD and clinical phenotype shows complete sex reversal from female to male. The sex-determining region Y (SRY) gene can be identified in most 46,XX testicular DSD patients; however, approximately 20% are SRY-negative. Here we present a 2 week old with discrepant prenatal karyotype and infant phenotype.

Case: This 2-week-old had dysmorphic features (bitemporal narrowing, broad and flat nasal bridge, bilateral epicanthal folds) and multiple congenital anomalies; IUGR, hypertelorism, cleft lip and palate, ASD, small kidneys, sacral dimple. Physical exam revealed palpable inguinal masses and microphallus without hypospadias. Postnatal karyotype showed a 46,XX chromosome complement with duplication of 22q13-qter. He was negative for SRY gene by FISH. Microarray analysis confirmed the duplication encompassing the SOX10 gene. Lab evaluation showed LH 10.81 mIU/ml, FSH 3.21 mIU/ml and total testosterone 241 ng/dl. These values are consistent with activation of the hypothalamic–pituitary–gonadal axis during the neonatal period in males.

Conclusion: Our case along with previous cases supports the existence of a gene on chromosome 22q that can trigger testis determination in the absence of SRY. Potential mechanisms responsible for ovotesticular disorder in the XX (SRY−) individual could involve activation of testis