pulmonary stenosis, global developmental delay, and constipation presented to the neurology clinic for evaluation of gross motor delay. She was found to have upper body part hypotonia, decreased reflexes, and on laboratory evaluation, severe hypercalcemia with Ca level of 15.0 mg/dL (8.7 - 10.7). The patient was admitted for management of severe hypercalcemia. Physical exam was also remarkable for subtle features of WS: a happy baby, very social, with prominent eyes, full cheeks, flat nasal bridge, round nasal tip, full lips, and a wide smile. Repeated Ca level on admission was 15.9 mg/dL, with normal albumin level of 4.6 g/dL (2.9-5.5), elevated ionized calcium (iCal) of 1.99 mmol/L (0.95 - 1.32), and intact parathyroid hormone (PTH) of <4.0 pg/mL (8.0 - 85.0). Further evaluation revealed a normal 25 hydroxy-vitamin D:41 ng/mL (30-80) and low 1,25-dihydroxy vitamin D:10pg/mL (31-87). Further evaluation revealed elevated urine calcium to creatinine ratio of 0.7 (normal for age <0.56) and renal ultrasound remarkable for medullary nephrocalcinosis. The patient had a complete blood count within normal limits and a PTH related protein of 26 pg/mL (14-27), ruling out malignancy. Hypercalcemia responded well to intravenous fluids and diuretics, the patient being discharged home after two days on furosemide and potassium supplements with close electrolytes monitoring. The patient required calcium reducing therapy for four months to maintain Ca levels within 9-12 range. The medication was decreased gradually based on calcium and ical levels. The patient is currently doing well, with a normal calcium level, and has being off medication for the past three months. **Conclusion:** This is a rare case of severe hypercalcemia, which led to the diagnosis of WS. Although idiopathic infantile hypercalcemia occurs in 15% of patients with WS, usually the presentation is mild, and the patients do not require medical interventions. Our patient presented with severe hypercalcemia and subtle physical features of WS that led to genetic testing and final diagnosis.

Adrenal

TRANSLATIONAL STUDIES ON ADRENOCORTICAL FUNCTION IN HEALTH AND DISEASE

Effects of Nonpeptide Orally Bioavailable ACTH Antagonists on Adrenal Gland Size and Function in Rats

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OR19-03

Cushing's disease (CD) and Ectopic ACTH syndrome (EAS) stem from excess circulating adrenocorticotropic hormone (ACTH) and resulting hypercortisolemia. In CD, excess ACTH is secreted from pituitary tumors, whereas excess ACTH in EAS arises from nonpituitary tumors. ACTH acts on the adrenal melanocortin type 2 (MC2) receptor to control the synthesis and secretion of adrenal hormones, including the stress hormone cortisol (corticosterone in rats) which accounts for the comorbidities of CD and EAS. Availability of a potent ACTH antagonist that can normalize cortisol in patients with diseases of excess ACTH will be a major advance in endocrinology. Additionally, an ACTH antagonist will have utility in congenital adrenal hyperplasia (CAH) because of its ability to block production of excess adrenal androgens.

Crinetics is evaluating and developing ACTH antagonists for the treatment of diseases of excess ACTH. To our knowledge, these compounds represent the first potent nonpeptide ACTH antagonists to demonstrate in vitro potency and in vivo efficacy. As a result, the direct effects of sustained MC2 receptor blockade on the structure and function of the adrenal gland have never been able to be assessed. We examined the effects of several orally bioavailable ACTH antagonists across a range of doses on Sprague-Dawley rat adrenal gland weight, histology, and hormone levels in repeat dosing (7-14 days) studies. Sustained MC2 receptor antagonism dose dependently blocked activity of ACTH at the level of the adrenal gland and reduced plasma corticosterone levels. In the normal rat, this resulted in dose-dependent atrophy of the adrenal gland as assessed by organ weights and microscopically. The atrophy was primarily observed in the cortisol producing zona fasciculata, as well as in the zona reticularis, with smaller reductions noted in the aldosterone producing zona glomerulosa. Additionally, hypertrophy of the adrenal glands caused by continuous subcutaneous administration of exogenous ACTH was reversed by treatment with an ACTH antagonist. The adrenal effects were accompanied by expected changes in corticosterone levels. These preclinical findings demonstrate the therapeutic potential of ACTH antagonism and provide a strong rationale for development of an orally bioavailable drug that can be used to combat CD, EAS, and CAH.

Pediatric Endocrinology

PEDIATRIC GROWTH AND ADRENAL DISORDERS

Early Adiposity Rebound in Youth with Congenital Adrenal Hyperplasia Predicts Childhood Obesity and Adiposity in Adolescence

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SAT-097

Purpose: Youth with classical Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency have an increased prevalence of obesity, abdominal adiposity, and fat mass compared to unaffected youth. As well, CAH youth in the United Kingdom (UK) have been found to have an earlier adiposity rebound (AR; rise in BMI corresponding to increased adipocyte size and number) at 1.7 years old, three years earlier than the general UK population. In unaffected youth, an earlier AR is predictive of obesity in adolescence. Our objective was to further understand the relationships between AR, weight status, and disease factors inherent to CAH in pediatric patients at our United States (US)

center. **Methods:** In 45 youth with classical CAH, weight-for-length (kg/cm; if <2 yr) percentiles or BMI (kg/m^2; if ≥2 yr) Z-scores were calculated every 6 months between the ages of 1 and 7 years, and at the patient's last clinic visit. The cubic polynomial method was used to determine age at AR, located at the nadir before the second rise in the model. BMI-Z at the last clinic visit (12.6±3.8 yr) was used to classify final weight status as lean (Z<2) or obese (Z≥2). AR, and weight-for-length percentile at 1 yr, were analyzed for prediction of BMI-Z at 7 yr. Additionally, in a subset of 21 CAH youth enrolled in prior studies, total body fat and trunk fat (DXA), as well as abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT; single-slice CT or 3-T MRI at the level of the umbilicus) were cross-sectionally measured. Other CAH factors assessed in all youth included: glucocorticoid dose at AR, 17OHP at newborn diagnosis, and average bone age SD from clinical x-rays. Mann-Whitney *U* tests and Pearson correlations were used to assess group differences and associations. Simple linear regressions were used to predict childhood obesity and adolescent adiposity. Data are presented as mean±SD. **Results:** Age at AR for CAH youth was 3.1±1.4 yr, which is earlier than the normative US population (5.5 yr). Stratifying youth by weight status at their last clinic visit, age at AR was earlier in obese (2.5±1 yr, n=23) versus lean (3.7±1.6 yr, n=22; p<0.01) youth. AR strongly predicted BMI-Z at 7 yr (R= -0.65, β= -0.27, p<0.001) whereas weight-for-length percentile did not (R=0.22, p=0.14). AR was negatively correlated with total body fat (R= -0.58, p<0.01), trunk fat (R= -0.60, p<0.01), and abdominal SAT (R= -0.60, p<0.01), but not with VAT (R= -0.24, p=0.3). There were no associations between AR and glucocorticoid dose or newborn 17OHP. However, AR was negatively correlated with bone age SD (R= -0.37, p=0.05). **Conclusion:** Youth with CAH at our center exhibited an earlier AR by two years compared to the normative US population. This earlier AR was predictive of obesity in childhood, as well as increased total body fat and central adiposity in adolescence. Further study of disease-specific factors such as genotype in CAH are merited.

Pediatric Endocrinology

PEDIATRIC OBESITY, THYROID, AND CANCER

Discovery and Identification of Late Stage Selective Nonpeptide Somatostatin Subtype 5 (sst5) Agonists for the Treatment of Hyperinsulinemic Hypoglycemia

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MON-089

Congenital hyperinsulinism (CHI) results from mutations within the insulin secretion pathway and is characterized by excessive and/or inappropriate insulin secretion by pancreatic islet β-cells. CHI is the most common cause of persistent hypoglycemia in newborns and infants and is estimated to affect 1:2500 to 1:50,000 live births. Prompt recognition and treatment are vital to prevent coma, long-term neurological complications, and even death. If medical control of CHI is unsuccessful, a near-total pancreatectomy may be required, but hypoglycemia often persists. The neuropeptide somatostatin is an important modulator of pancreatic hormonal signaling and activity at different somatostatin receptor (sst) subtypes dictates the suppression of insulin and/or glucagon. The injectable peptide drugs octreotide and lanreotide are potent sst2 agonists used to treat CHI, but in addition to suppressing insulin, the sst2 activity of these peptides may also inhibit glucagon secretion, potentially reducing effectiveness and compromising a key defense against hypoglycemia. Glucagon secretion from α-cells is inhibited through activation of sst2 receptors, while insulin secretion from β-cells is inhibited through activation of sst2 and sst5. We therefore hypothesize that agonists selectively targeting sst5 and lacking sst2 activity will offer an improved efficacy/safety profile for patients with hyperinsulinemic hypoglycemia.

Using iterative medicinal chemistry and pharmacology, Crinetics has discovered several classes of highly potent, orally bioavailable, small molecule sst-subtype selective agonists with drug-like pharmaceutical properties. Our discovery efforts aimed at finding a compound to treat CHI have yielded potent and selective nonpeptide sst5 agonists with sub-nanomolar EC_{50}s in cell-based assays of receptor activation. Insulin secretion from isolated human and rat islets was suppressed upon exposure to sst5 agonists. Potent and selective sst5 agonists were then evaluated in a number acute and repeat dose in vivo models (e.g., oGTT, fed/fasted conditions, sulfonylurea-induced hypoglycemia) to assess physiological effects and to gain mechanistic insights. As predicted by the in vitro pharmacology, selective nonpeptide sst5 agonists suppressed insulin secretion and raised blood glucose levels in each model, while having minimal effects on glucagon secretion. Leading sst5 agonists were also evaluated for drug like characteristics, including stability in liver microsomes, lack of inhibition of cytochromes P450 and the hERG ion channel, and were shown to exhibit good exposure upon oral dosing in both rats and dogs. The culmination of these studies has led to a subset of candidate molecules that are being evaluated in genotoxicity, safety pharmacology, and general toxicity studies to determine the molecule most suitable for evaluation in human clinical trials.

Pediatric Endocrinology

PEDIATRIC ENDOCRINE CASE REPORTS I

A Rare Case of Primary Hyperparathyroidism in a Pediatric Patient

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SAT-058

Introduction: Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder in adult patients, but it is rare in pediatric patients. It is usually diagnosed when patients present with symptomatic hypercalcemia or known complications. In children, atypical presentation