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