The following abstracts from The Journal of Clinical Endocrinology & Metabolism have been selected by the editors of Endocrinology as being particularly relevant to readers interested in translational science.

**Treatment with Recombinant Human Insulin-Like Growth Factor (rhIGF)-I/rhIGF Binding Protein-3 Complex Improves Metabolic Control in Subjects with Severe Insulin Resistance**

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(*J Clin Endocrinol Metab, 10.1210/jc.2009-2088*)

**ABSTRACT**

**Objective:** Diabetes in the context of severe insulin resistance (SIR) presents a major therapeutic challenge because conventional therapies including insulin and insulin sensitizers often fail to achieve adequate metabolic control. Adjunctive therapy with recombinant human IGF-I (rhIGF-I)/recombinant human IGF binding protein-3 (rhIGFBP-3) has been shown to improve insulin sensitivity in both type 1 and type 2 diabetes and may have a role in the treatment of SIR. We report clinical and physiological outcomes after adjunctive therapy with rhIGF-I/rhIGFBP-3 in five subjects with SIR.

**Research Design and Methods:** Five females (median age, 17 yr; range, 5-37) with SIR (two with pathogenic insulin receptor mutations) were treated with 0.5-2.0 mg/kg rhIGF-I/rhIGFBP-3 using a 16-wk dose escalation protocol. Glycosylated hemoglobin was recorded monthly, and at baseline and end of treatment all patients were evaluated using continuous glucose monitoring sensing and admitted for overnight GH profiling and insulin-modified stable-label iv glucose tolerance test. Changes in body composition were assessed using dual-energy x-ray absorptiometry and magnetic resonance imaging.

**Results:** Treatment with rhIGF-I/rhIGFBP-3 was well tolerated, and all subjects reported clinical improvements with reduction in acanthosis nigricans. Glycosylated hemoglobin was reduced (8.5% pretreatment to 7.1%; P<0.03) with a trend toward reduction in mean continuous glucose monitoring sensing glucose (10.7 vs. 8.5 mmol/liter; P = 0.08). Effects of treatment on other biochemical measures were variable, but there was a trend toward improved C-peptide responses during the iv glucose tolerance test.

**Conclusions:** rhIGF-I/rhIGFBP-3 is well tolerated and clinically effective in subjects with SIR.

**TAC3/TACR3 Mutations Reveal Preferential Activation of GnRH Release by Neurokinin B in Neonatal Life Followed by Reversal in Adulthood**


(*J Clin Endocrinol Metab, 10.1210/jc.2009-2320*)

**ABSTRACT**

**Context:** Mutations in TAC3 and TACR3 (encoding neurokinin B and its receptor) have been identified in Turkish patients with hypogonadotropic hypogonadism (IHH), but broader populations have not yet been tested and genotype-phenotype correlations have not been established.

**Objective:** A broad cohort of normosmic IHH probands was screened for mutations in TAC3/TACR3 to evaluate the prevalence of such mutations and define the genotype/phenotype relationships.

**Design:** Sequencing of TAC3/TACR3; in vitro functional assays, neuroendocrine phenotyping.

**Setting:** Tertiary care centers world-wide.

**Patients or other participants:** 345 probands, 18 family members, 292 controls.

**Intervention:** Examination of reproductive phenotypes throughout reproductive life and pre/post therapy.

**Main Outcome Measure:** Rare sequence variants in TAC3/TACR3.
Results: In TACR3, 19 probands harbored 13 distinct coding sequence rare nucleotide variants (3 nonsense mutations, 6 non-synonymous, 4 synonymous [one predicted to affect splicing]). In TAC3, one homozygous single base pair deletion was identified, resulting in complete loss of the neurokinin B decapeptide. Phenotypic information was available on 16 males and 7 females with coding sequence variants in TACR3/TAC3. Of the 16 males, 15 had microphallus; none of the females had spontaneous thelarche. Seven of the 16 males and 5/7 females were assessed after discontinuation of therapy and 6/7 males and 4/5 females demonstrated evidence for reversibility of their hypogonadotropism.

Conclusions: Mutations in the neurokinin B pathway are relatively common as causes of hypogonadism. While the neurokinin B pathway appears essential during early sexual development, its importance in sustaining the integrity of the hypothalamic-pituitary-gonadal axis appears attenuated over time.

Mutations of the KISS1 Gene Associated with Central Precocious Puberty
(J Clin Endocrinol Metab, 10.1210/jc.2009-2421)

Abstract
Context: Kisspeptin, encoded by the KISS1 gene, is a key stimulatory factor of GnRH secretion and puberty onset. Inactivating mutations of its receptor (KISS1R) cause isolated hypogonadotropic hypogonadism (IHH). A unique KISS1R activating mutation was described in central precocious puberty (CPP).

Objective: To investigate KISS1 mutations in patients with idiopathic CPP and normosmic IHH.

Patients: Eighty-three children with CPP (77 girls) and 61 patients with IHH (40 men) were studied. The control group consisted of 200 individuals with normal pubertal development.

Methods: The promoter region and the 3 exons of KISS1 were amplified and sequenced. Cells expressing KISS1R were stimulated with synthetic human wild-type or mutant kisspeptin-54 (kp54) and inositol phosphate accumulation was measured. In a second set of experiments, kp54 was pre-incubated in human serum prior to stimulation of the cells.

Results: Two novel KISS1 missense mutations, p.P74S and p.H90D, were identified in three unrelated children with idiopathic CPP. Both mutations were absent in 400 control alleles. The p.P74S mutation was identified in the heterozygous state in a boy who developed CPP at 1 yr of age. The p.H90D mutation was identified in the homozygous state in two unrelated girls with CPP. In vitro studies revealed that the capacity of the P74S and H90D mutants to stimulate IP production was similar to the wild-type. After pre-incubation of wild-type and mutant kp54’s in human serum, the capacity to stimulate signal transduction was significantly greater for P74S compared to the wild-type, suggesting that the p.P74S variant is more stable. Only polymorphisms were found in the IHH group.

Conclusion: Two KISS1 mutations were identified in unrelated patients with idiopathic CPP. The p.P74S variant was associated with higher kisspeptin resistance to degradation in comparison to the wild-type, suggesting a role for this mutation in the precocious puberty phenotype.

Infants of Women with Polycystic Ovary Syndrome have Lower Cord Blood Androstenedione and Estradiol Levels
Helen Anderson, Naomi Fogel, Stefan K. Grebe, Ravinder J. Singh, Robert L. Taylor, and Andrea Dunaif
(J Clin Endocrinol Metab, 10.1210/jc.2009-2651)

Abstract
Context: Prenatal androgen excess can cause a phenocopy of polycystic ovary syndrome (PCOS) in mammals. Retrospective studies have suggested that girls at risk for PCOS have low birth weight and prospective studies have suggested an increased prevalence of small for gestational age offspring in women with PCOS.

Objective: To determine whether infants of women with PCOS have reduced birth weight or increased intrauterine androgen levels.

Design: Prospective case-control study.

Participants: Thirty-nine PCOS and 31 control women and their infants.