Main Outcome Measures: Measures of executive function, memory, and spatial cognition were obtained before and after treatment. Hormone levels were obtained 10 times over the course of the study.
Results: Counter to expectations, hormone treatment did not affect cognition (ps $>$ 0.10). Free testosterone was positively related to spatial cognition in older men after treatment and controlling for age and estradiol level or exclusion of the hypogonadal men ($P = 0.02$). Estradiol was negatively associated with working memory controlling for the same variables ($P = 0.01$). Blinding to treatment assignment was maintained, with the exception of the hypogonadal group.
Conclusions: A significant change in sex hormone status, including complete hypogonadism, does not modify cognition in men. These findings, along with studies that show a risk for neurodegenerative disease in those with low testosterone, suggest that sex hormone status may be important for neuroprotection in aging but not modulation of normal day-to-day cognitive function.

Associations between Body Composition, Circulating Interleukin-1 Receptor Antagonist, Osteocalcin, and Insulin Metabolism in Active Acromegaly

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ABSTRACT

Objective: Patients with active acromegaly display a range of abnormalities in glucose metabolism. To elucidate interactions between bone and energy homeostasis in relation to excess GH, we sought to determine whether these patients were characterized by alterations in circulating levels of adipokines and cytokines and potential interactions with osteocalcin (OCN) and insulin resistance.
Methods: Forty-seven patients with active acromegaly: 26 women and 21 men (49 $\pm$ 11, mean $\pm$ SD) were evaluated and compared with age-, sex-, and body mass index-matched controls by x-ray absorptiometry, biochemical analysis [GH, IGF-I, OCN, leptin, adiponectin, retinol binding protein 4, IL-6, IL-1β, and IL-1 receptor antagonist (IL-1Ra)], and glucose metabolism (homeostasis model assessment). *In vitro* effects of GH/IGF-I on IL-1β/IL-1Ra in THP-1 macrophages and human white adipocytes as well as effects of GH/IGF-I in combination with carboxylated and undercarboxylated OCN on glucose-stimulated insulin release in human pancreatic islets were also investigated.
Results: Patients with acromegaly were characterized by markedly decreased serum levels of IL-1Ra and increased IL-1β and IL-1β to IL-1Ra ratio, suggesting enhanced IL-1 activity. The decreased IL-1Ra was strongly associated with increased OCN levels in multivariate models and was significantly correlated with decreased total body fat mass. In macrophages, IGF-I/GH significantly decreased the release of IL-1Ra and increased IL-1β, suggesting that the decreased circulating IL-1Ra levels in acromegaly could reflect both direct and indirect mechanisms. Finally, circulating OCN was the main determinant of insulin resistance and β-cell function in acromegaly and *in vitro*, a blunted insulin response was observed in the presence of OCN and GH/IGF-I.
Conclusion: These data confirm and establish novel and complex interactions between bone, energy metabolism, and adipose tissue and suggest an unfavorable effect of OCN and GH/IGF-I in combination on insulin metabolism in active acromegaly.

Unraveling the Directional Link between Adiposity and Inflammation: A Bidirectional Mendelian Randomization Approach

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ABSTRACT

Context: Associations between adiposity and circulating inflammation markers are assumed to be causal, although the direction of the relationship has not been proven.
Objective: The aim of the study was to explore the causal direction of the relationship between adiposity and inflammation using a bidirectional Mendelian randomization approach.

Methods: In the PROSPER study of 5804 elderly patients, we related C-reactive protein (*CRP*) single nucleotide polymorphisms (SNPs) (rs1800947 and rs1205) and adiposity SNPs (*FTO* and *MC4R*) to body mass index (BMI) as well as circulating levels of CRP and leptin. We gave each individual two allele scores ranging from zero to 4, counting each pair of alleles related to CRP levels or BMI.
Results: With increasing *CRP* allele score, there was a stepwise decrease in CRP levels (P for trend < 0.0001) and a 1.98 mg/liter difference between extremes of the allele score distribution, but there was no associated change in BMI or leptin levels ($P \geq 0.89$). By contrast, adiposity allele score was associated with 1) an increase in BMI (1.2 kg/m^2 difference between extremes; P for trend 0.002); 2) an increase in circulating leptin (5.77 ng/ml difference between extremes; P for trend 0.0027); and 3) increased CRP levels (1.24 mg/liter difference between extremes; P for trend 0.002).
Conclusions: Greater adiposity conferred by *FTO* and *MC4R* SNPs led to higher CRP levels, with no evidence for any reverse pathway. Future studies should extend our findings to other circulating inflammatory parameters. This study illustrates the potential power of Mendelian randomization to dissect directions of causality between intercorrelated metabolic factors.

Acute Tissue Injury Caused by Subcutaneous Fat Biopsies Produces Endoplasmic Reticulum Stress

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ABSTRACT
Background: It is not known whether acute tissue injury is associated with endoplasmic reticulum (ER) stress.
Objective: Our objective was to determine whether open, sc fat biopsies cause ER stress.
Approach: Five healthy subjects underwent three open sc fat biopsies. The first biopsy, taken from the lateral aspect of a thigh, was followed 4 h later by a second biopsy from the same incision site and a third biopsy from the contralateral leg. Expression markers of ER stress, inflammation, hypoxia, and adipokines were measured in these fat biopsies. In addition, we tested for signs of systemic ER stress and inflammation in plasma and in circulating monocytes.
Results: mRNA/18s ratios of IL-6, monocyte chemoattractant protein-1, CD-14, hypoxia-induced factor 1-α, the spliced form of Xbox protein-1, glucose-regulated protein 78, CEBP homologous protein, and activating factor-4 were all severalfold higher, whereas mRNA/18s ratios of adiponectin and leptin were lower in fat biopsies taken from the same site 4 h after the first biopsy but were unchanged in the second biopsy that was taken from the contralateral site. The biopsies were not associated with changes in plasma and monocyte IL-6 concentrations or in monocyte ER stress markers. Also, whole-body insulin-stimulated glucose uptake was the same in 15 subjects who had biopsies compared with 15 different subjects who did not.
Conclusion: Open, sc fat biopsies produced inflammation, hypoxia, ER stress, and decreased expression of adiponectin and leptin. These changes remained confined to the biopsy site for at least 4 h.

Critical Roles of Kisspeptin in Female Puberty and Preovulatory Gonadotropin Surges as Revealed by a Novel Antagonist

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ABSTRACT
Kisspeptins (Kp) have recently emerged as master regulators of the reproductive axis and among the most potent elicitors of GnRH-gonadotropin secretion. Despite their paramount importance in reproductive physiology and their potential therapeutic implications, development of Kp antagonists has remained elusive, and only recently has the first compound with the ability to block Kp actions *in vitro* and *in vivo*, namely p234, been reported. However, previous *in vivo* studies all used acute central injections, whereas characterization of the effects of the antagonist after continuous or systemic administration, which poses pharmacological challenges, is still pending. We report herein a comprehensive series of analyses on the impact of continuous intracerebroventricular infusion of p234 on puberty onset and the preovulatory surge of gonadotropins in the female rat. In addition, the effects of systemic (ip) administration of a tagged p234-penetratin, with a predicted higher permeability at the blood-brain barrier, on Kp-10 induced gonadotropin secretion were evaluated. Central infusion of p234 to pubertal females delayed vaginal opening and decreased uterine and ovarian weights at the expected time of puberty, without affecting body weight. Likewise, chronic intracerebroventricular administration of p234 for 4 d prevented the preovulatory surges of LH and FSH. In addition, systemic (ip) administration of p234-penetratin significantly attenuated acute LH and FSH responses to Kp-10, either after intracerebroven-