This contrasts the strong association of insulin resistance with non-alcoholic fatty liver disease in the general population. Acromegaly may therefore help to elucidate antisteatotic pathways. Since low HCL in acromegaly might be caused by changes in oxidative substrate metabolism and interorgan crosstalk we investigated mitochondrial activity and plasma metabolomics as well as lipidomics in active acromegaly.
Approach & Results
Patients In this cross-sectional study, 15 patients with active acromegaly (ACRO) and 17 healthy controls (CON) matched for age, BMI, gender and body composition were included. All participants were invited to undergo 31P/1H-7T-MR-spectroscopy of the liver and skeletal muscle, as well as plasma metabolomic profiling and an oral glucose tolerance test.
In comparison to CON, ACRO were insulin resistant, and showed significant lower HCL but their hepatic ATP-synthesis rate adjusted to HCL was significantly increased (h_kATP:0.19[0.14;0.24]vs0.28[0.22;0.34] s-1);p=0.024). Furthermore, the HCL-adjusted ratio of unsaturated to saturated intracellular fatty acids was decreased in ACRO (8.4%vs25.5% of HCL,p<0.04). In skeletal muscle, intramyocellular lipids and ATP-synthesis rate were significantly decreased in ACRO. Plasma lipids and lipidomics did not differ between ACRO and CON, but decreased levels of carnitine species were observed in ACRO.
Conclusions
The dissociation of hepatic lipid content and peripheral insulin resistance in acromegaly is associated with high mitochondrial activity as indicated by liver specific upregulation of the ATP-synthesis rate. This is paralleled by a decreased ratio of unsaturated-to-saturated lipids in hepatocytes and by a change in circulating carnitine species, also reflecting an increased mitochondrial activity. Our findings hint at potential direct effects of growth hormone excess on hepatic lipid and energy metabolism.

Pediatric Endocrinology

PEDIATRIC OBESITY, THYROID, AND CANCER

Modulator of Gut Barrier, Zonulin Was Associated with Waist to Height Ratio in Adolescents

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MON-109
Modulator Of Gut Barrier, Zonulin Was Associated With Waist To Hip Ratio In Adolescents
Background: Zonulin is the endogenous protein known to control the permeability of intestinal tight junction reversibly. Zonulin is actively engaged in intestinal innate immunity and is over-expressed in autoimmune diseases where tight junction of intestine plays a pivotal role, such as celiac disease, malabsorption disorder, and type 1 diabetes. Waist-Height ratio was well known as one of indices of obesity and also Waist-Hip ratio was known of abdominal obesity. We investigated that the associations among Waist-Height, Waist-Height ratio, and the level of Zonulin by assessing obesity-related biomarkers, such as liver enzymes, lipid profiles, and insulin resistance, in a population of adolescents.
Methods: The study included 198 adolescents aged 12-18 years; 92 were overweight/obese and 106 were of normal-weight. We assessed anthropometric and laboratory measures, including body mass index (BMI), BMI z-score, Waist-Height, Waist-Hip ratio, blood pressure, liver enzyme levels, lipid profiles, and insulin sensitivity. Serum Zonulin levels were measured using an enzyme-linked immunosorbent assay.
Results: The mean age of the participants was 15.2±2.5 years. Circulating serum Zonulin levels were significantly increased in overweight/obese participants compared with those in normal-weight participants (P=0.042). Zonulin levels were significantly and positively associated with BMI, BMI z-score, alanine aminotransferase levels, triglyceride, fasting insulin, and insulin resistance as indicated by the homeostasis model assessment of insulin resistance (HOMA-IR) (all P<0.05). In multivariate linear regression analysis, alanine aminotransferase (P<0.0001), triglyceride (P<0.0001), and HOMA-IR (P=0.001) contributed independently to circulating Zonulin levels after controlling for the effect of BMI z-score. Zonulin levels were more strongly associated with Waist-Hip ratio rather than Waist-Height ratio.
Conclusions: Zonulin was associated with indices of obesity. Waist-Hip ratio was more strongly associated with levels of Zonulin. The positive correlation between these parameters suggests putative pathophysiological mechanism linking Zonulin to metabolic dysfunction in adolescents.

Neuroendocrinology and Pituitary

ADVANCES IN NEUROENDOCRINOLOGY

Brain-Selective Estrogen Therapy to Prevent Androgen Deprivation Therapy-Related Hot Flushes

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SUN-234
Synthetic estrogens are used in the clinic to alleviate debilitating neurological symptoms associated with androgen deprivation therapy (ADT), an effective treatment improving survival in prostate cancer patients when administered timely in the course of the cancer. However, this therapy to relieve the symptoms, most commonly hot flushes, causes feminizations that significantly diminishes patients' compliance because of physical and psychological discomfort. Because only estrogens can provide adequate therapy of hot flushes based on current clinical practices, there is an unmet medical need for an effective, side effect-free and, consequently, compliance-gaining intervention to alleviate these vasomotor symptoms distressing prostate cancer patients on ADT. The goal with our experiments was

to show that treatment with 10β,17β-dihydroxyestra-1,4-dien-3-one (DHED, a brain-selective bioprecursor prodrug of 17β-estradiol (E2) will ease ADT-associated hot flushes without feminizing side-effects.
To evaluate the effect of DHED on hot flushes the pharmacological rat hot flush model was used. Orchiectomized (ORDX) rats were treated orally with three different doses (10, 30, and 100 μg/kg) of DHED or ethynyl estradiol (EE, 200 μg/kg) for ten days. They were addicted to morphine and the tail skin temperature (TST) of saline-treated rats raised by 4.4±0.5 °C when morphine effect was withdrawn with naloxone injection. DHED and EE treatments significantly lowered such TST rise from 4.4 °C to 2.9 ±0.5°C and 1.8 ±0.5°C, respectively.
The conversion of DHED to E2 in the brain was confirmed by measuring the effect of DHED-derived E2 on the expression of progesterone receptors (PR) in the preoptic area of the hypothalamus with *in situ* hybridization histochemistry. Both DHED and EE treatment stimulated PR expression compared to saline-treatment in ORDX rats.
In our previous studies, we have shown the lack of conversion of DHED to E2 in the periphery in ovariectomized female rats; i.e., DHED treatment did not have uterotrophic, mammotrophic activities and did not stimulate galanin expression in the anterior pituitary. In these studies, the lack of conversion of DHED to E2 was also confirmed in male rats by measuring the expression of galanin, a highly estrogen-regulated gene, in the pituitary with quantitative RT-PCR. Contrary to EE, DHED treatment did not stimulate galanin expression in this estrogen target.
These observations support subsequent translational research focusing on DHED's therapeutic use to remedy hot flushes and potentially other neurological symptoms in prostate cancer patients undergoing ADT to manage their malignancy. An estrogen therapy with the brain-selective DHED would provide a safe approach to prevent these neurological symptoms without causing peripheral estrogenic side effects such as gynecomastia or deep vein thrombosis.

Diabetes Mellitus and Glucose Metabolism

ISLETS, LIVERS, PLACENTA, AND VASCULATURE — THE MULTITISSUE IMPACT OF DIABETES

FSTL3 Neutralizing Antibodies Restore Function to Diabetic Mouse and Human Islets: A New Approach for Treating Diabetes

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OR14-01

Activin, GDF11 and myostatin are structurally related members of the TGFbeta superfamily of growth factors with many biological roles in animal models and humans. Their actions are neutralized by extracellular proteins such as follistatin and follistatin like-3 (FSTL3). We have previously demonstrated that genetic inactivation of *Fstl3* results in enlarged pancreatic islets containing increased numbers of beta cells that produce more insulin in response to glucose compared to wild type litter mates. We further discovered that at least some of these new beta cells arise via transdifferentiation from alpha cells. We also demonstrated that functional human islets from normal donors produce very high levels of activin. In contrast, activin biosynthesis is vastly reduced and FSTL3 synthesis is significantly increased in human islets from diabetic donors suggesting that activin is critical for normal insulin production. This was substantiated by direct treatment of human diabetic islets with activin which restored their response to glucose. These observations support the hypothesis that an FSTL3 neutralizing antibody would constitute a novel therapeutic approach to curing diabetes through restoring beta cell function as well as accelerating generation of new beta cells through transdifferentiation. To test this hypothesis, we produced a mouse monoclonal antibody that neutralized hFSTL3 (FP-101), thereby releasing bioactive activin, GDF11, and myostatin. We have now tested this antibody for biological activity in vitro on mouse and human islets. We used islets from high fat diet (HFD) treated *mice* to model diabetes-inducing effects of obesity as well as 24-hour incubation in hyperglycemic (33 mM glucose) medium to create *human* islets that lose responsiveness to high glucose as a model for human diabetes. In mouse islets we found that stimulation of normal (chow diet) islets by high glucose produced a stimulation index (SI) of 3.5 that was reduced to 2 in HFD islets. Treatment with activin, FP-101, or a commercial polyclonal antibody to mFSTL3 all increased response of HFD islets to elevated glucose and partially restored SI to normal levels. In human islets, hyperglycemia eliminated the normal (2.5 SI) response to high glucose while activin or FP-101 treatments dose-responsively restored this response. These results demonstrate that anti-FSTL3 therapy can restore function to compromised beta cells from mouse and human diabetes models. The observation that activin has the same action as anti-FSTL3 antibody indicates that FP-101 works through enhancing the activin signaling pathway. Finally, these results demonstrate that the FSTL3-activin pathway is an important regulator of beta cell function in humans as well as mice, supporting further development of this therapy as a diabetes treatment.

Genetics and Development (including Gene Regulation)

ENDOCRINE DISRUPTING CHEMICALS

Region-Specific Effects of the Exposome on Brain Monoamine Levels in Female Rats

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SAT-717

Prenatal programming with endocrine disrupting chemicals (EDCs), in particular the ubiquitous plasticizers