for tyrosine hydroxylase (th), a key enzyme in CA synthesis, results in embryonic lethality likely due to the lack of dopamine and norepinephrine in the CNS where they serve as key neurotransmitters.

Here we studied the role of the SNS and catecholaminergic signaling in metabolic control in both aging as well as high fat diet (HFD) induced obesity. We created a mouse model of inducible th gene deletion that is restricted to the periphery, including sympathetic fibers of the peripheral NS but spares the brain as a pharmaco-genetic model of sympathectomy(2). TH is deleted and CA levels were reduced more than 90% in peripheral tissues of TH KO mice, while intact in the CNS. TH KO mice are cold intolerant consistent with functional sympathectomy. Interestingly, TH KO mice are protected from HFD feeding induced glucose intolerance (AUC during GTT: WT1018.8±42.0 mg/dl/hr vs. TH KO 485.0±85.8 mg/dl/hr; p < 0.0001; n = 6) even though food intake increased in TH KO mice. In 20 months old TH KO mice glucose tolerance was improved and fasting blood glucose levels were reduced (AUC during GTT: WT 357.3±16.2 mg/dl/hr vs. TH KO 254.5±15.6 mg/dl/hr; p < 0.01; n = 12) with higher insulin levels (WT 0.35±0.07 μg/l vs. TH KO 1.28±0.28 μg/l; p < 0.001; n = 9). Of note, insulin tolerance tests did not show marked differences. Both obesity and aging are characterized by impaired adipose tissue function with reduced lipogenic capacity. TH KO mice fed a HFD exhibit increased WAT de novo lipogenesis, lower lipolysis, and trend to exhibit decreased adipose tissue inflammation, suggesting that the SNS is a major culprit for the impaired lipogenic capacity in adipose tissue. Our data provides support for the paradigm that impaired SNS function plays an important role in the dysmetabolic states of obesity and aging.

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Adipose Tissue, Appetite, and Obesity

Adipose Tissue Biology and Obesity II

Adipocyte Specific Endothelin a Receptor Knockout Increases Adiposity in Mice

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SUN-592

Obesity is associated with increased levels of Endothelin-1 (ET-1). Blockade of ET-1 type A receptors (ET\textsubscript{A}) improves lipid profile in patients with chronic kidney disease; however the mechanism is unknown.[1] In adipocytes ET\textsubscript{A} activation increases lipolysis, a potential mechanism for elevated lipids in obese individuals.[2] Therefore, the goal of this study was to determine if adipocyte specific knockout (KO) of the ET\textsubscript{A} receptor in mice alters genes associated with lipid metabolism in adipose and improves plasma lipids. 24-week old adipocyte ET\textsubscript{A} knockout mice had significantly elevated body weight compared to floxed controls (32.6±1.0 vs. 29.5±0.7 g respectively). Echo MRI revealed that the increased body weight was due to greater adiposity (10.12±0.9 vs. 14.7±1.8 % body weight; floxed vs. KO), while no statistical difference was observed in lean weight (88.9±2.4 vs. 86.8±2.6 % body weight; floxed vs. KO). Surprisingly, there were no statistical differences in plasma total cholesterol or triglycerides. RNA sequencing indicated downregulation of 597 genes and upregulation of 444 genes in visceral adipose and downregulation of 368 and upregulation of 847 genes in subcutaneous adipose. KEGG pathway analysis revealed that most genes altered in visceral adipose were related to metabolic pathways. These data implicate a role for adipose tissue ET\textsubscript{A} receptors in regulating adiposity and promoting pathophysiology related to obesity.

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Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING I

Reciprocal Regulation of miR-375 and ICER in Pancreatic Beta Cells

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SUN-718

MicroRNA-375 (miR-375) is overexpressed in people with type 2 diabetes (T2D) and has been linked to decreased insulin secretion and beta cell proliferation. Investigation into the transcription factor inducible cAMP early repressor (ICER) as an intermediate regulator of miR-375 was proposed because both are regulated by the cAMP pathway. This overexpression of miR-375 in T2D led us to hypothesize that beta cells with elevated and reduced levels of miR-375 will result in decreased and increased glucose-stimulated insulin secretion (GSIS), respectively. Results showed that when miR-375 was overexpressed, GSIS decreased by 61% when compared to a control in 25 mM glucose. Results showed that when miR-375 was inhibited, GSIS increased 6% when compared to a control in 25 mM glucose. In human islets, we found that inhibiting miR-375 led to an average 19% increase in GSIS, though due to the variability of human tissue these
data were not significant (N=5). To investigate ICER’s binding affinity to the miR-375 promoter, a luciferase reporter assay was conducted. HEK-293 (human embryonic kidney) cells that were transfected with a luciferase reporter plasmid containing a cAMP recognition element (CRE) and a plasmid driving the overexpression of ICER had a 75% decrease when compared to our control (P<0.05). When transiently-expressed ICER was knocked down via siRNA, promoter activity increased by 13.1-fold (P<0.05). Using a chromatin immunoprecipitation assay we found that an ICER antibody pulled down the rat miR-375 promoter an average of 13-fold compared with a control antibody (N=2). Additionally, because of a sequence alignment showing possible binding of miR-375 to the human ICER transcript we hypothesize that the two are in a negative feedback loop and can regulate each other’s expression. To investigate the double negative feedback loop a plasmid was constructed containing the GFP reporter gene and either the human or rodent ICER 3’UTR predicted miR-375 binding site. The GFP reporter assay was conducted to determine if miR-375 binds to ICER’s microRNA recognition element (MRE) in a species-specific way. In our GFP reporter experiment, data shows there is a 50% reporter gene decrease between our negative control and the human ICER MRE (N=4, P=0.017). Understanding microRNA gene regulation in the pancreas may have important implications for patients with T2D. MiR-375 may have the ability to interact with human ICER in a double negative feedback loop in the cAMP second messenger pathway, which will further clarify cellular mechanisms to potentially improve T2D drugs.

Reproductive Endocrinology

TRANSGENDER MEDICINE AND RESEARCH

Male Pattern Baldness and Waist-Hip Ratio as Markers of Arterial Stiffness in Transgender Men Undergoing Long-Term Testosterone Therapy.

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SUN-049

Introduction: Association between male pattern baldness, also called androgenetic alopecia (AGA) and risk of coronary artery disease has been suggested by several epidemiological studies. Exogenous testosterone (T) therapy in transgender men (TM) promotes the development of alopecia in genetically susceptible individuals, and increases facial and body hair, muscle mass (MM) and visceral fat. The outcome of a long-term androgenic therapy over the functional properties of large arteries and the cardiovascular system of TM are not well established. Objective: To investigate the possible association between AGA and arterial stiffness assessed by measurement of carotid-femoral pulse wave velocity (VOPcf) and intima-media thickness carotid artery (cIMT) in TM receiving long-term T therapy. Methods: Forty-six TM (mean age: 43 ± 10 yo) undergoing T therapy (mean time of treatment duration: 13 ± 10 y; mean serum T levels: 611 ± 439 ng/dL) were evaluated in a cross-sectional study. Hair pattern (Ferriman & Gallway scale), grades of male pattern baldness (Hamilton-Norwood scale) and waist-ratio (WHR) were analyzed. Subjects were considered to have AGA if they have vertex alopecia (grade ≥ 3). Arterial Hypertension was defined as systolic blood pressure > 140 and/or diastolic blood pressure > 90mmHg or under pharmacological treatment, and dyslipidemia as total cholesterol ≥ 240 mg/dL and/or LDL-c ≥ 160 mg/dL and/or HDL-c < 40 mg/dL and/or triglycerides > 200 mg/dL, or under pharmacological treatment. Current smoking has been investigated. The aortic stiffness, assessed by VOPcf and cIMT, was measured using the Complior® device and carotid ultrasound, respectively. Results: TM’s Ferriman degree was 21 ± 6 and AGA was identified in 70% of them. The WHR was 0.9 ± 0.1. TM with AGA showed higher cIMT than TM without AGA (0.66 ± 0.1mm vs. 0.54 ± 0.07mm, p = 0.001), as well as higher WHR (0.93 ± 0.08 vs. 0.87 ± 0.04, p = 0.02), higher score in terminal body hair (Ferriman 23 ± 6 vs. 18 ± 6, p = 0.007) and higher frequency of hypertension (94% vs. 6%, p = 0.01). The cIMT positively correlated with age (p = 0.01) and WHR (p = 0.002). The VOPcf was positively correlated with the age (p = 0.0001), androgen treatment duration (p = 0.01) and WHR (p = 0.04). There was a positive correlation between androgen treatment duration and WHR (p = 0.01). There was no difference in the VOPcf values, age, T treatment duration, serum T levels, frequency of dyslipidemia and smoking between the groups. Conclusion: The severe vertex AGA pattern may be considered a possible marker of arterial stiffness in TM undergoing long-term testosterone therapy.

Thyroid

THYROID DISORDERS CASE REPORTS II

Myxedema Coma Mimicking Cardiogenic Shock Treated with Levothyroxine

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Myxedema coma is a medical emergency with a mortality rate of 30–50%. It is a commonly missed diagnosis and can lead to multiple cardiovascular complications which are reversible with levothyroxine treatment. IV levothyroxine

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