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

Osvaldo Rivera-Gonzalez, MS, Joshua S. Speed, PhD.
University of Mississippi Medical Center, Jackson, MS, USA.

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Obesity is associated with increased levels of Endothelin-1 (ET-1). Blockade of ET-1 type A receptors (ET_A) improves lipid profile in patients with chronic kidney disease; however the mechanism is unknown.[1] In adipocytes ET_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_A receptor in mice alters genes associated with lipid metabolism in adipose and improves plasma lipids. 24-week old adipocyte ET_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 (10.1±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_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

Stephanye Frias, BS, Ryan Nielsen, BS, Isis Perez, BS, Jesse Garcia, BS, David M. Keller, PhD.
California State Univ, Chico, CA, USA.

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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