

Federal University of Santa Catarina, Florianopolis-SC, Brazil.

#### MON-624

**Introduction:** Physical activity plays an important role in glycemic control in patients with type 2 diabetes, but overall adherence rate is low. For patients not able or willing to engage in regular physical exercise, whole body vibration comes as a potential alternative. **Objective:** To evaluate the effect of 28Hz whole body mechanical vibration on glycemic control and other metabolic parameters in patients with type 2 diabetes. **Methods:** 24 adults with type 2 diabetes on oral antidiabetic agents, with a baseline HbA1c between 6.5 and 9.0%, were randomized into two groups. The control group (CG) was advised to adopt lifestyle modifications, and the intervention group (IG) received the same orientations and used a 28 Hz whole body vibrating platform daily for 20-30 minutes during 12 weeks. **Results:** Data from 22 patients were analyzed (one from each group was excluded). Baseline characteristics of both groups were similar except for triglycerides, which were higher in the CG (111.8±39.9 mg/dL vs. 188.9±68.8 mg/dL, p<0.05). After 12 weeks, there was a significant reduction in glycated hemoglobin in the IG (7.69±0.49 vs. 7.17±0.77%, p<0.05), not observed in the CG (8.05±0.98 vs. 7.92±1.07%, p=0.52). A non-significant trend for weight loss in IG was observed (78.14±10.47 vs. 77.14±11.08Kg, p=0.069). There were no significant differences between the groups regarding fasting blood glucose or any other clinical and biochemical variables analyzed. **Conclusion:** This study suggests an improvement in glycated hemoglobin at 12 weeks with the use of the 28Hz vibration platform in patients with type 2 diabetes. However, further studies with a larger number of patients and longer follow-up are needed to better define the role of whole body vibration as an adjuvant in glycemic control.

## Thyroid

### THYROID HORMONE ACTION AND SIGNALING

#### *Kruppel-Like Factors 9 and 13 Cooperate to Maintain Mammalian Neuronal Differentiation*

Jose Avila-Mendoza, PhD, Arasakumar Subramani, MS, Robert J. Denver, PhD.

University of Michigan, Ann Arbor, MI, USA.

#### OR01-04

During development of the central nervous system, neural cells respond to several external cues that influence cell proliferation, differentiation, axonal growth and synaptogenesis. Thyroid hormone plays a critical role in each of these processes. Previously, we showed that Krüppel-like factor 9 (KLF9), a zinc finger transcription factor, is strongly and directly induced by liganded thyroid hormone receptors, and it mediates the actions of thyroid hormone on neuronal differentiation during late fetal development. Here we analyzed the molecular mechanisms by which KLF9 maintains neuronal structure, and inhibits regeneration in juvenile and adult neuronal cells. We also investigated the actions of the closely related transcription factor KLF13, which is paralogous to KLF9. We engineered the adult mouse hippocampus-derived cell line HT22 to control *Klf9* or *Klf13* expression by addition of doxycycline.

We also used CRISPR/Cas9 genome editing to generate *Klf9* or *Klf13* knock out (KO), and *Klf9+Klf13* double KO HT22 cell lines. To induce neurite outgrowth, we treated cells with forskolin (FK)+IBMX, which increases intracellular cAMP; elevated cAMP is a hallmark of regenerative responses of neurons to injury. Our results show that FK+IBMX increased neurite length in the parent HT22 cell line, and this action was enhanced in *Klf9* and *Klf13* single KO cells, and was even greater in double KO cells. By contrast, the stimulatory effect of FK+IBMX on neurite outgrowth was blocked by simultaneous forced expression of *Klf9* or *Klf13* in parent HT22 cells. This effect on neurite outgrowth was confirmed in primary mouse hippocampal neurons, where electroporation of expression plasmids for *Klf9* or *Klf13* suppressed FK+IBMX-induced neurite extension compared with empty vector-transfected cells. Analysis of RNA-seq data obtained from HT22 cells following 8 hr of induced *Klf9* or *Klf13* expression showed that both proteins impact the cAMP signaling pathway. Using transfection-reporter assays and chromatin immunoprecipitation, we confirmed that several genes in this pathway are direct targets of both KLFs. Our findings suggest that KLF9 and KLF13 may cooperate to maintain the differentiated state of mammalian neurons and thereby block regeneration, in part, by repressing the cAMP signaling pathway.

## Cardiovascular Endocrinology

### HYPERTRIGLYCERIDEMIA; INFLAMMATION AND MUSCLE METABOLISM IN OBESITY AND WEIGHT LOSS I

#### *Extremely Elevated Plasma Lipoprotein X Level Secondary to Alcoholic Cholestasis*

Carolyn Ann Nelson, MD, Zahid Ahmad, MD, Abhimanyu Garg, MD.

University of Texas Southwestern Medical Center, Dallas, TX, USA.

#### SAT-572

##### Background

Marked elevations of plasma lipoprotein X (Lp-X) levels have been reported in patients with cholestasis due to primary biliary cirrhosis, pancreatic cancer, hepatitis C, and quetiapine. We now report a patient with extreme elevation of plasma Lp-X due to alcohol-induced cholestasis.

##### Case Presentation

A 44 year-old African American male presented with painless jaundice and fatigue for one week. He denied nausea, vomiting, diarrhea, change in stool or urine color, or weight loss. He consumes 720-1080 mL of beer (2-3 cans) every night and admitted to heavier alcohol consumption in the past. On physical examination he had scleral icterus and hepatomegaly but no xanthomas or xanthelasmas.

His serum total cholesterol was 1,126 mg/dL (normal range, 120-199 mg/dL), triglycerides were 238 mg/dL (50-150 mg/dL), calculated LDL-cholesterol was 1,072 mg/dL (<100 mg/dL), and HDL-cholesterol was 6 mg/dL (>39 mg/dL). His serum AST, 162 IU/L (10-50 IU/L); ALT, 79 IU/L (10-50 IU/L); alkaline phosphatase, 1,058 IU/L (40-129 IU/L); total bilirubin, 18.8 mg/dL (0.2-1.3 mg/dL); direct bilirubin, 13.5 mg/dL (0-0.3 mg/dL); and gamma glutamyl transferase, 4,583 IU/L (8-61 IU/L) were markedly elevated. His blood alcohol

level was 34 mg/dL (not detected), sodium 124 mmol/L (135-145 mmol/L), and platelet count was 84,000/ $\mu$ L (150,000-459,000/ $\mu$ L). His TSH 2.89  $\mu$ IU/mL (0.4-4.5  $\mu$ IU/mL), UA without proteinuria, HBV immunized, HCV negative, and anti-mitochondrial antibody negative. CT abdomen revealed hepatic steatosis and gallbladder swelling without evidence of obstruction. MRCP showed cirrhosis without primary sclerosing cholangitis. Serum lipoprotein electrophoresis confirmed the presence of Lp-X. On day 3 of hospitalization, his cholestasis improved and his serum total bilirubin 10.0 mg/dL, direct bilirubin 7.4 mg/dL, AST 108 IU/L, ALT 66 IU/L, and alkaline phosphatase 663 IU/L had improved. The patient was advised to abstain from all alcohol consumption. Telephone follow up 2 months later with his wife revealed that he had stopped drinking alcohol and that his jaundice had resolved.

#### Conclusions

Although alcohol-induced cholestasis is a well-recognized entity, such presentation with extreme elevations of Lp-X has not been previously reported. In such patients, it is important to establish whether extreme hypercholesterolemia is due to LDL or Lp-X since, as opposed to LDL, Lp-X elevations are not considered to be atherogenic.

## Diabetes Mellitus and Glucose Metabolism

### METABOLIC INTERACTIONS IN DIABETES

#### *Hyperinsulinemia Suppresses Hepatic Autophagy at Late Sepsis in an mTOR-Dependent Transcriptional Regulation*

Chin Hsu, PhD<sup>1</sup>, Li-Fang Wang, PhD<sup>2</sup>

<sup>1</sup>Department of Physiology, Kaohsiung, Taiwan, <sup>2</sup>Department of Medicinal and Applied Chemistry, College of Life Science, KMU, Kaohsiung, Taiwan.

#### SUN-667

Hyperinsulinemia Suppresses Hepatic Autophagy at Late Sepsis in an mTOR-dependent Transcriptional Regulation

**Abstract:** Autophagy transiently occurs in the liver at early stage, while autophagy suppression associated with liver failure occurs at late stage in a CLP (cecal ligation and puncture) model of sepsis. However, the factors that cause autophagy suppression at late sepsis remain unknown. Hyperinsulinemia is observed in early sepsis, and insulin inhibits autophagy via mTOR, which regulates TFEB/ZKSCAN3 nuclear translocation and the transcription of autophagy-related genes (LC3, p62, WIPI2, ATG9 etc.). Thus, we used CLP mouse model of sepsis to test the hypothesis that early hyperinsulinemia suppresses late hepatic autophagy via the mTOR-dependent transcriptional regulation of autophagy-related genes. The results showed that hyperinsulinemia occurs 3 h after CLP (CLP3h) and is followed by mTOR phosphorylation and autophagy suppression at the late stage (CLP9~15h) of sepsis. The administration of HNMPA, an insulin receptor antagonist, decreases mTOR/ULK-1 (unc-51 like autophagy activating kinase 1) phosphorylation and relieves autophagy suppression in late sepsis. Encapsulated rapamycin, which blocks hepatic mTOR/ULK-1 signaling downstream of insulin, enhances the nuclear translocation of TFEB in early sepsis, increases the protein expression of autophagy-related genes

(LC3 and p62) and relieves autophagy suppression in late sepsis. Moreover, rapamycin rescues hepatic dysfunction and increases the survival rate after CLP. These results suggest that early hyperinsulinemia suppresses hepatic autophagy in late sepsis in an mTOR-dependent manner. Nothing to Disclose: LW, PC, YL, CH

## Reproductive Endocrinology

### FEMALE REPRODUCTION: BASIC MECHANISMS

#### *Chronic Resveratrol Exposure Improves Glucose Homeostasis and Cardiac Function in a Rat Model of Polycystic Ovarian Syndrome.*

Rogelio Enrique Molina, BS<sup>1</sup>, Tiffany Shao, BS<sup>1</sup>, Harmanprit Randhawa, BS<sup>1</sup>, Vanessa Hoang, BS<sup>2</sup>, Arpita Kalla Vyas, MD<sup>1</sup>.

<sup>1</sup>California Northstate, Elk Grove, CA, USA, <sup>2</sup>Michigan State University, Lansing, MI, USA.

#### MON-028

Chronic resveratrol exposure improves glucose homeostasis and cardiac function in a rat model of Polycystic Ovarian Syndrome.

**Abstract:** Polycystic ovary syndrome (PCOS) is the commonest endocrinopathy in women of reproductive age, with a prevalence of 5-8%. Long-term complications seen in PCOS include cardiovascular disease and type 2 Diabetes Mellitus. Current therapies do not completely address the cardiometabolic perturbations seen in women with PCOS. Resveratrol (RSV), a natural polyphenol, is shown to have beneficial cardio-metabolic effects in various pathological conditions including that on insulin sensitivity, cardiovascular function. In-vitro studies suggest it's beneficial effects on ovarian function as well. Therefore, we hypothesized that chronic exposure to RSV would improve both cardiovascular and metabolic phenotypes in PCOS. To test this hypothesis we used an established rat model of PCOS that develops metabolic derangement and irregular cycles. A 7.5 mg (90-day release) dihydrotestosterone (DHT) pellet providing a daily dose of 83 mcg was implanted in 5-week-old female rats. Studies were also conducted on littermate matched controls (C) with no DHT implant. A subgroup of the control and DHT treated rats (n=6 per group) received a 0.84 g/kg dose of resveratrol (RSV) in their chow starting at age 5 weeks. At 8 weeks, animals were weighed weekly (n=6 per group). Oral glucose tolerance test (OGTT n=6 per group) and cardiac echocardiogram (C n=12, C+RSV n=6, DHT n=10, DHT+RSV n=6) were conducted at 16-weeks of age. Body weight increased significantly in DHT treated rats compared to C between 8 and 16 weeks (40 vs 22 grams, p <0.001). RSV treatment did not mitigate the effects of DHT on body weight (34 vs 40 grams, p>0.5). There was significantly higher glucose excursion at 30 minutes post glucose load in both DHT (148 $\pm$  7.4 mg/dl) and DHT+RSV (139 $\pm$  7.4 mg/dl) compared to C group (121 $\pm$  13 mg/dl, p<0.001, p=0.03 respectively). However, by 60 and 90 minutes only DHT group had a significantly higher glucose excursion compared to both DHT+RSV and C groups (131 $\pm$  4.1, 124 $\pm$  5.7, 110 $\pm$  5.9 mg/dl, p=0.015, p=0.21 respectively); 90min (118 $\pm$  5.8, 110 $\pm$  4.7, 96 $\pm$  4.2 mg/dl, p<0.01, p=0.09 respectively). By 120 minutes, no significant difference in glucose levels existed between groups. Cardiac echocardiogram showed significantly lower mitral valve E/A ratio