

Thursday November 5, 3:45-5:15 PM

T-OR-2057

Metformin Counters a Pro-Inflammatory T Cell Profile in Obesity

Barbara Nikolajczyk *Boston Massachusetts*, Min Zhu *Boston MA*, Nicholas Cilfone *Cambridge Massachusetts*, Forum Raval, Jose Cacicedo *Boston MA*, Douglas Lauffenburger *Cambridge MA*, Caroline Apovian *Boston MA*

Background: Reports disagree on whether the diabetes drug metformin impacts obesity-associated type 2 diabetes (T2D) by activating anti-inflammatory mechanisms that include the metformin target AMPK.

Methods: We compared the effect of metformin on inflammation and AMPK activation in PBMCs and T cells from 3 groups of people with obesity: normoglycemic (ND), pre-T2D or fulminant T2D. Half of the pre-T2D and all the T2D subjects took metformin (500mg 2x/daily; N=8/group). We stimulated T cells (+/- additional metformin) in the context of PBMCs from all subjects and quantified cytokine production by bioplex. We used cytokine-by-cytokine analyses and multivariate mathematical methods, including principal components and partial least squares analyses, to identify T cell cytokine profiles for each sample. Western blots or extracellular flux analysis quantified AMPK/AMPK targets or oxygen consumption.

Results: Single cytokine comparisons showed many inflammatory T cell cytokines were maximally expressed by T2D samples, despite more AMPK activation and oxygen consumption in T cells from T2D compared to ND samples. Multivariate analyses showed Th17 cytokines uniquely separated T2D cytokine profiles from pre-T2D or ND profiles, and that Th2 cytokines were surprisingly critical to separate ND from pre-T2D profiles. In vitro metformin blunted production of single cytokines ($p<0.05$) in all samples, but only at supra physiological concentrations. In contrast, projection of cytokine profiles from pre-T2D samples exposed to metformin in vivo onto the multivariate model showed profiles from 5 (of 8) subjects clustered with ND profiles. Surprisingly, in vivo metformin did not alter AMPK in pre-T2D.

Conclusions: T cell cytokine profiles differentiate subjects with obesity according to metabolic health. A majority of pre-T2D subjects on metformin have less inflammatory profiles, similar to Th2 profiles of ND subjects. The anti-inflammatory action of in vivo metformin occurs in the absence of increased AMPK activation.

T-OR-2058

Perilipin 5 (Plin5) Deletion Alters Skeletal Muscle Lipid and Glucose Metabolism

Ruzaidi Azli Mohd Mokhtar *Clayton VIC*, Clinton Bruce *Burwood VIC*, Matthew Watt *Clayton Not required for this country*

Background: Plin5 is a lipid droplet associated protein that is highly expressed in oxidative tissues, such as skeletal muscle and heart, and plays a major role in regulating lipid metabolism in most tissues. The aim of this study was to delineate the role of Plin5 in regulating substrate metabolism in muscle.

Methods: Lipid and glucose metabolism were assessed by radiometric methods in primary myotubes produced from wild-type and whole body Plin5 null mice. Mice with conditional targeted deletion of Plin5 in skeletal and cardiac muscle were

generated by Cre-Lox approaches and used to examine metabolism in muscle in vivo. Wild-type (Wt) and Plin5 muscle-specific knockout (Plin5MKO) mice were fed either a chow or a high-fat diet (HFD) for 12 weeks before experiments.

Results: Plin5 deletion did not affect the oxidation or storage of extracellular-derived fatty acids, glucose oxidation or glycogen synthesis in vitro but did remodel the intracellular lipid pool, resulting in increased ceramide content. Plin5MKO mice had normal body weight, food intake and energy expenditure. The respiratory exchange ratio was reduced in Plin5MKO mice, demonstrating an increase in whole-body fatty acid oxidation and decrease in carbohydrate oxidation. Intriguingly, fatty acid and glucose oxidation were not different between genotypes when assessed in skeletal muscle ex vivo. In mice fed a HFD, glucose tolerance was markedly better in Plin5MKO compared with Wt mice and this was associated with increased glucose clearance without changes in endogenous glucose production.

Conclusions: Plin5 ablation increases intracellular lipolysis and remodels the skeletal muscle lipidome, without marked effects on glucose metabolism in vitro. In contrast, Plin5 ablation enhances glucose disposal in the setting of rodent obesity in vivo. This mismatch in glucose metabolism and the discrepancy between whole-body and skeletal muscle fatty acid oxidation suggests that Plin5 ablation may alter endocrine signalling to modulate whole body metabolism.

T-OR-2059

Endurance exercise affects adipose tissue fatty acid storage across different metabolic conditions

Kazanna Hames *Rochester Minnesota*, Shichun Du *Shanghai Shanghai*, Lendia Zhou *Rochester MN*, Barbara Norby *Rochester MN*, Michael Jensen *Rochester MN*

Background: We sought to examine how exercise affects free fatty acid (FFA) storage in subcutaneous (SQ) fat depots across metabolic conditions, and examine how this relates to markers of the fat storage pathway.

Methods: FFA storage rates in abdomen and thigh SQ fat were measured in sedentary adults (n=9; VO₂peak: 38.2±4.1 ml/min/kg FFM) and endurance athletes (n=9; VO₂peak: 55.6±6.0 ml/min/kg FFM) under conditions of (1) high FFA (732±188 μM) using somatostatin to suppress insulin (0.2±0.1 uIU/ml) while fasted, and (2) reduced plasma FFA (319±92 μM) created by fatty meal ingestion to raise insulin (9.7±5.5 uIU/ml). Continuous infusions of [U-13C]palmitate and [U-13C]linoleate traced FFA kinetics and boluses of [3H] and [14C]palmitate combined with biopsies measured SQ fat FFA storage. We assayed for adipocyte acyl-CoA synthetase (ACS) and diacylglycerol acetyltransferase (DGAT) activity.

Results: The sedentary adults increased abdomen SQ fat palmitate storage rates by 47% from the fasted to fed state (p=0.04), while the athletes did not change palmitate storage rates in this depot (p=0.41; across groups: p=0.19). Sedentary adults also increased thigh SQ fat palmitate storage rates by 27% from the fasted to fed state (p=0.05), while again the athletes had no change (p=0.20; across group: p=0.02). This resulted in almost double the palmitate storage rates in thigh SQ fat in the sedentary adults (0.55±0.22 μmol/min/kg lipid) compared to the athletes (0.29±0.14 μmol/min/kg lipid; p=0.01). Changes in adipocyte ACS and DGAT activity did not explain the differences in SQ fat FFA storage rates across metabolic conditions within or across groups.

Conclusions: We expected sedentary adults to have greater SQ fat FFA storage than athletes, particularly during the fasted state's high FFA conditions. However, our results indicated

sedentary adults had greater FFA storage only in thigh SQ fat during the fed state's low FFA conditions. The mechanism for differences in SQ fat's FFA storage is yet identified.

T-OR-2060**Quantitation of dietary fat incorporation into intramuscular lipid species in humans**

Qiong Hu *Columbia Missouri*, Phillip Sanders *Indianapolis Indiana*, Miriam Jacome-Sosa *Columbia Missouri*, Ming-Shang Kuo *Indianapolis IN*, Sudha Shankar *Cranford New Jersey*, Elizabeth Parks *Columbia MO*

Background: Elevated lipid content in skeletal muscle contributes to insulin resistance. Thus far, no reports have compared the quantitative contributions of dietary saturated (SatFA) and monounsaturated fat (MUFA) to intramuscular lipid pool. The goal of the present study was to develop a method to quantify the rate of incorporation of dietary fat into skeletal muscle lipids in humans.

Methods: Nondiabetic adults (n=4, 2M, 2F, BMI 24.8 ± 4.6 kg/m²) were fed a high-fat breakfast and lunch of identical composition (40% fat, 42% CHO, 17% protein), and underwent vastus lateralis muscle biopsies before (fasting) and 9-h after the two meals. A stable isotope (d31-palmitate or d34-oleate) was added to the meals to label triglyceride-rich lipoproteins (TRL). Infusion-based quadruple time-of-flight (Q-TOF) mass spectrometry was used to analyze the triglyceride (TG) labeling pattern in TRL and in muscle biopsy samples. TRL-TG enrichment was used as the precursor pool to calculate muscle lipid fractional synthesis rate (FSR).

Results: Intramuscular TG (IMTG) contents ranged from 0.98-1.26 mg/g wet weight in the fasting state, and 0.77-1.33 mg/g in the fed state. The FSR of IMTG from dietary fat ranged from 0.31%/h-1.13%/h, which was, surprisingly, higher than reported synthesis rates of IMTG from the plasma FFA pool (0.28%/h). The isotope enrichment and labeling pattern were measured in other muscle lipid species, and desaturation and elongation products of d31-palmitate were detected. IMTG FSR was higher when SatFA was fed in the meal.

Conclusions: In summary, these data demonstrate the extent to which dietary fat can directly and significantly contribute to intramuscular lipid synthesis. This methodology could be applied to determine how dietary fat composition (SatFA vs MUFA) influences muscle lipid handling and impacts insulin sensitivity.

T-OR-2061**Regulatory Processes in the Cellular Uptake of Long Chain Fatty Acids (LCFA).**

Fengxia Ge, José Walewski *New York New York*, Mehvar Torghabeh *New York NY*, Gregory Dakin *New York NY*, Alfons Pomp *New York NY*, Dieunine Anglade *New York NY*, Faith Ebel *New York NY*, Paul Berk *New York New York*

Background: Background: The principal process by which LCFA enter adipocytes is facilitated transport, an important control point for adiposity. While large adipocytes from obese subjects take up LCFA faster than small non-obese cells, the relative contributions to LCFA uptake of cell size per se, regulated expression of LCFA transport machinery, and other processes remain unclear.

Methods: Methods: We obtained omental & subcutaneous fat biopsies & blood samples at each operation from 10 super-obese (SO) participants in a 2-stage bariatric surgical study. Ten non-obese (NO) surgical patients & 10 obese (O) bariatric surgical patients were controls. Adipocyte suspensions were isolated from each biopsy, and mean cell surface areas (SA) &

cell volumes determined. 3H-Oleic acid uptake kinetics were studied to define the V_{max} for LCFA uptake (pmol/sec/50,000 cells) and to compute V_{max}', defined as V_{max}/SA (pmol/sec/μ² of adipocyte SA), a measure of the plasma membrane density of LCFA transport "machinery".

Results: Results: [1] Pre-operatively V_{max} increased exponentially ~8- fold as a function of BMI (BMI 20-73, r=0.86, p<0.01). [2] V_{max}' also increased exponentially by ~3-fold. [3] During a >1 year post-surgical weight loss of ~120 lbs, V_{max} decreased by 40%, remaining within the range associated with obesity, but adipocyte sizes in many patients fell into the normal range. The greater proportional decline in SA than in V_{max} therefore resulted in an overall increase in V_{max}' in those patients.

Conclusions: Conclusions: [1] When LCFA uptake data are expressed per cell (e.g. V_{max}), a single variable, V_{max}, quantitatively dominates the process. [2] Expressed per cell surface area (e.g. V_{max}') the result depends on both the total cellular uptake capacity and the cell surface area. [3] The current data suggest that some degree of regulation of adipocyte size may be independent of LCFA uptake and intracellular lipid accumulation.

T-OR-2062**Activation of mTORC1 in Muscle Results in Increased Intramyocellular Glycogen and Triglycerides Along with Reduced Adiposity**

Dave Bridges *Memphis Tennessee*, Erin Stephenson *Memphis TN*, JeAnna Redd *Memphis TN*, Matthew Peloquin *Orlando FL*, Binbin Lu, Kathryn Cyrus *Memphis TN*, Alan Saltiel

Background: mTORC1 is a nutrient sensing kinase expressed in many tissues. mTORC1 has been implicated in lipid storage, insulin sensitivity and glycogen accumulation. mTORC1 is activated in muscle tissues both in normal conditions such as growth and after a meal, but its activity is also elevated in chronic conditions including obesity and aging.

Methods: We generated mice in which mTORC1 is activated in muscle tissue, by deleting its negative regulator TSC1. We then tested whether these mice had any changes in both muscle-specific and systemic changes in glucose or carbohydrate homeostasis. We also evaluated transcriptional changes in these muscles by RNA sequencing.

Results: We found that the muscles from these mice had elevated triglycerides and glycogen, the latter of which was associated with increases in the glycogenic enzyme PTG. With respect to triglycerides we did not observe any elevations in lipogenic enzymes, or reductions in beta-oxidation enzymes but we did observe and up regulation of fatty acid transport machinery. In contrast to our expectations, these animals had normal insulin sensitivity, though they did have a reduced glucose tolerance. We evaluated glucose-stimulated insulin secretion and found that these mice had impaired insulin release after a glucose injection. We also found that these mice have dramatically reduced adiposity.

Conclusions: Endurance athletes have paradoxical elevations in both intramyocellular glycogen and triglycerides but no decreases in insulin sensitivity. We have generated an animal model that mimics these effects. These results also implicate muscle and mTORC1 signaling in particular in the regulation of obesity as these animals have reduced fat mass, potentially due to partitioning of lipids to the muscle for oxidation rather than storage in adipose tissue. Finally, these studies point to a previously undescribed process by which muscle can directly regulate insulin secretion.

T-OR-2063

Sex Differences in the Association of Body Mass Index with Anatomical Architecture of Reward Network Regions in Healthy Subjects

Arpana Gupta *Los Angeles California*, Emeran Mayer *Los Angeles California*, Mher Alaverdyan *Los Angeles CA*, Connor Fling *Los Angeles CA*, Claudia Sanmiguel *Los Angeles California*, Kirsten Tillisch *Los Angeles CA*, Jennifer Labus *Los Angeles CA*

Background: Recent advances in computationally intense mathematical algorithms has made it possible to characterize the architecture of regions in large-scale brain networks within obesity. The most fundamental network measures are degree and local clustering efficiency, which are associated with increased transfer of information between regions.

Methods: 99 subjects completed diffusion tensor imaging scans. Regional parcellation was conducted and resulted in 74 bilateral cortical and 7 subcortical structures, including the cerebellum. Relative fiber density between regions was obtained. Anatomical network metrics were constructed from the thresholded correlation matrix. A general linear model was applied to examine the influence of sex, BMI, and sex*BMI interaction on the degree and local efficiency of the extended reward regions.

Results: There were 57 lean and 42 non-lean individuals. BMI was positively associated with degree of left thalamus ($\beta=1.14$), left caudate ($\beta=.67$), and right nucleus accumbens ($\beta=.83$), but negatively associated with right ventromedial prefrontal cortex ($\beta=-.62$). BMI was positively associated with local efficiency for right amygdala ($\beta=.009$) and left nucleus accumbens ($\beta=.008$), but negatively associated with right anterior insula ($\beta=-.006$), and right ventromedial prefrontal cortex ($\beta=-.007$). For degree, there was a significant interaction effect for right dorsolateral prefrontal cortex ($\beta=-1.39$) with males and not females; and a significant interaction for right nucleus accumbens ($\beta=-.66$) with females but not males. For local efficiency there was a significant interaction for left hippocampus ($\beta=-.005$) with males but not females.

Conclusions: The anatomical network architecture of regions within the reward network is associated with BMI. Findings indicate that higher BMI and being female is associated with more local and regional communication between regions involved in dopamine signaling, and less information propagation was observed in the cognitive frontal regions.

T-OR-2064

Obesity-Related Proinflammatory Environment is Associated with Variations in the Brain's Reward System Architecture

Claudia Sanmiguel *Los Angeles California*, Arpana Gupta *Los Angeles California*, Jennifer Labus *Los Angeles CA*, Iordanes Karagiannides *Los Angeles CA*, Kirsten Tillisch *Los Angeles CA*, Mger Alaverdyan *Los Angeles CA*, Kristen Coveleskie *Los Angeles CA*, Cody Ashe-McNalley *Los Angeles CA*, Jean Stains *LA CA*, Suzanne Smith *Los Angeles CA*, Lin Chang *Los Angeles CA*, Emeran Mayer *Los Angeles California*

Background: Multivariate analyses are able to discriminate between individuals with normal and high BMI based on morphological brain measures. The mechanisms behind these differences are not well understood. A plausible explanation is the presence of a proinflammatory environment affecting the brain's structure. Hypothesis: 1) Overweight/Obese (O/O) subjects display differences in the reward network's architecture when compared to lean subjects 2) Brain morphometric differences are related to adipokines levels

Methods: 37 adult subjects (26 females) - 22 lean (BMI: 21.8 ± 1.7) and 15 O/O subjects (BMI: 29 ± 4.9) - underwent brain MRIs. Freesurfer analysis yielded 165 parcellated regions with 4 gray matter (GM) metrics: volume (V); cortical thickness; surface area; mean curvature. A magnetic bead-based multiplex assay measured serum adipokines levels. Pearson correlations explored associations between GM measures, adipokines and BMI. General linear models examined interactions of obesity with adipokines on GM parameters.

Results: 1) BMI positively correlated with Leptin and GM metrics of the insula (INS) and posterior cingulate cortex (PCC), and negatively with the orbital frontal gyrus (OFG) and Adiponectin. 2) Leptin correlated positively with anterior CC and INS. 3) Monocyte chemoattractant protein 1 (CMP-1) correlated positively with PCC, INS, amygdala, frontal cortex and post-central gyrus. 4) IL-1 β , IL-6 and IL-8 correlated negatively with INS. 5) Higher BMI was associated with lower V in parahippocampal gyrus ($F=5.8$, $p=0.02$), and OFG ($F=12.8$, $p=0.001$). With increasing Adiponectin levels, women had smaller posterior cingulate gyrus and larger OFG V ($F=6.7$, $p=0.01$).

Conclusions: Higher BMI was related to greater Leptin levels and lower GM volume in the parahippocampus and OFC. Larger OFC volumes were seen with increasing levels of Adiponectin. Adipokine-related differences in brain's reward system architecture could result in anomalous top-down regulation of food-related behaviors and possibly lead to obesity.

T-OR-2065

Energy density influences interaction between FTO and DRD2 gene variants in brain reward system responses to food evaluation

Andrianos Yiorkas *London NA*, Christina Prechtl, Michelle Sleeth, Alexander Miras *LONDON LONDON*, Samantha Scholtz *London London*, Giuliana Durighel *LONDON LONDON*, Suzanne Alberts *Amsterdam Noord-Holland*, Gary Frost *London Al*, Jimmy Bell *London London*, Alexandra Blakemore *London London*, Anthony Goldstone *London*

Background: Genetic variants near the Fat mass and obesity-associated (FTO) gene are associated with obesity and consumption of energy-dense foods. We investigated the hypothesis that FTO genotype influences dopaminergic reward systems. We examined the interaction of an FTO obesity-associated single nucleotide polymorphism (SNP) and dopamine receptor D2 (DRD2) SNP, associated with altered dopaminergic signalling, on anticipatory food reward.

Methods: 45 European Caucasian adults (age 19-55 years, BMI 19.1-53.1 kg/m²) had functional magnetic resonance imaging (fMRI) during evaluation of food pictures after an overnight fast, to measure food appeal and BOLD signal in brain regions involved in reward processing: nucleus accumbens, caudate, anterior insula, amygdala, orbitofrontal cortex (OFC). DNA genotyping assessed carrier status of FTO rs9939609 A and dopamine receptor D2 (DRD2) TaqA1 alleles.

Results: FTO A carriers had greater BOLD signal to high-energy foods in OFC in whole brain analysis, and greater high-energy food appeal rating and external eating behaviour (independent of age, gender and percentage body fat). DRD2 A1 carriers had greater reward system responses to low-energy foods, particularly in caudate and nucleus accumbens. In gene-food interaction analysis, FTO A carrier status increased reward system responses to high-energy, but not low-energy foods, but only in DRD2 A1 non-carriers. Similarly DRD2 A1

carriers had greater reward system responses only to high-energy foods and only in FTO A non-carriers. Similar interactions were seen in an expanded mixed ethnicity cohort of 75 adults.

Conclusions: These results support a role for the FTO gene in regulation of body weight by altering human food reward processing through influences on dopaminergic neuronal function.

T-OR-2066

A pilot study with the synthetic peptide RM-493, a melanocortin-4 receptor (MC4R) agonist, for the treatment of heterozygous MC4R deficiency obesity

Keith Gottesdiener *Boston MA*, Hillori Connors *Boston MA*, Lex Van der Ploeg *Boston MA*, Sadaf Farooqi *Cambridge Cambridgeshire*, Tinh-Hai Collet *Cambridge Cambridgeshire*, Karine Clement *Paris France*, Béatrice Dubern *Paris NA*, William Lewis *Dallas TX*

Background: The hypothalamic Leptin-Proopiomelanocortin (POMC)-MC4R pathway is a critical regulator of appetite and weight. Monogenic defects in the POMC and the downstream MC4R gene lead to severe early onset obesity. Similarly, in Prader-Willi Syndrome (PWS), where the function of genes such as MAGEL2 are impaired, the Magel2^{-/-} mouse model revealed decreased POMC neuronal functioning as one critical mechanism of severe obesity in PWS. The MC4R agonist peptide RM-493, a first in class, well-tolerated and efficacious MC4R agonist, is ideally positioned to bypass genetic deficiencies in this pathway. To test this hypothesis, we conducted a pilot study in patients with a heterozygous MC4R deficiency, who represent 1-3% of the obese population.

Methods: Obese (BMI>30kg/m²) patients with a heterozygous MC4R loss of function mutation were enrolled in a pilot, double-blind, placebo (pbo) controlled, randomized, parallel group study for 4 weeks. Eight patients (6 active/2 pbo) received pbo or RM-493 at 0.01 mg/kg/day (~ 1 mg/day) by continuous subcutaneous infusion. Key endpoints were safety, weight loss, waist circumference (WC) and caloric intake.

Results: RM-493 was well tolerated over 4 weeks, with no SAEs or discontinuations. The most common side effects were headache and skin tanning (the latter due to off-target activity at the related MC1R). RM-493 demonstrated strong trends for placebo-subtracted weight loss (2.62 kg; p=0.08); WC (5.1 cm; p=0.188) and daily caloric intake (351 kCal/day; NS), without measurable effects on heart rate or blood pressure.

Conclusions: In this small pilot study, 4-week clinical data suggest that the MC4R agonist RM-493 leads to weight loss in obese patients with a genetic MC4R deficiency. This result will need to be confirmed in larger studies, and in trials in patients with other genetic defects in this important pathway where the spectrum of partial and full loss of function mutations that may differentially impact clinical outcomes can be understood.

T-OR-2067

Greater Hunger and Less Restraint Predict Weight Loss Success with Phentermine Treatment

Elizabeth Thomas *Aurora Colorado*, Bryan McNair, Jamie Bechtell *Aurora CO*, Annie Ferland *Aurora CO*, Marc-Andre Cormier *Aurora CO*, Robert Eckel *Aurora Colorado*

Background: Phentermine is the most widely prescribed weight loss medication, but individual response to treatment is variable. As phentermine is thought to cause weight loss through a reduction in hunger and subsequent energy intake, we hypothesized that higher subjective ratings of hunger would

be predictive of greater weight loss with phentermine treatment.

Methods: This is an observational pilot study in which all subjects were treated with phentermine hydrochloride 30mg daily for 8 weeks. Subjective ratings of appetite (hunger, satiety, desire to eat, and prospective food consumption [PFC]) were measured with visual analog scales prior to and after a test breakfast meal, as well as before meals at home for 3 days, at baseline and at week 8. In addition, eating behaviors (hunger, disinhibition and cognitive restraint [CR]) were measured with the Three Factor Eating Questionnaire at baseline and week 8. Appetite ratings and eating behaviors were compared in subjects with ≥5% vs <5% weight loss, and linear regression was used to identify predictors of percent weight loss.

Results: 27 healthy obese adults (37 ± 4.5 yrs, 93.8 ± 12.1 kg, BMI 33.8 ± 3.1 kg/m²) completed the study, with a mean weight loss of -5.4 (-11.8, 1.1) kg or -5.7 ± 3.2%. Subjects with ≥5% weight loss had higher baseline pre-breakfast hunger (p=0.017), desire to eat (p=0.003), and PFC (0.006), and lower baseline CR (p=0.01). In addition, higher baseline home PFC (p=0.002) and greater reduction in PFC at week 8 (p=0.017) predicted greater weight loss, as did lower baseline CR (p=0.001) and greater increase in CR at week 8 (p=0.026).

Conclusions: These results suggest that individuals reporting greater hunger and less restraint are more likely to achieve significant weight loss with phentermine treatment. This information can be used clinically to help determine which patients should be treated with phentermine, and to avoid the risks of treatment in patients unlikely to respond.

T-OR-2068

Phase 2 Trial of Beloranib, a Methionine Aminopeptidase 2 (Metap2) Inhibitor, Demonstrated Improved Cardiometabolic Profile with Weight Loss in Patients with Hypothalamic Injury-Associated Obesity

Ashley Shoemaker *Nashville TN*, Joseph Proietto *Heidelberg Victoria*, M Jennifer Abuzzhab *Saint Paul MN*, Tania Markovic *Sydney NSW*, Jaret Malloy *Boston MASSACHUSETTS*, Dennis Kim *Boston Massachusetts*

Background: Patients with hypothalamic injury-associated obesity (HIAO) fail to regulate metabolism and food intake, resulting in severe treatment-resistant obesity and associated comorbidities. In preclinical and clinical studies of obesity, beloranib reduced body weight (BW) and hunger with reduction of fat biosynthesis and stimulation of lipolysis and fat oxidation.

Methods: This was a randomized, double-blind, placebo-controlled study in 14 adults with HIAO. Patients received twice weekly SC doses of beloranib 1.8 mg (n=8) or placebo (PBO; n=6) for 4 wks followed by a 4 wk open label extension where all patients received beloranib 1.8 mg.

Results: Thirteen of 14 patients (9 females, age 31.9 yr, BMI 42.8 kg/m², BW 126.4 kg) completed the study with 12 patients comprising the per protocol population (beloranib n=8; PBO n=4). After 4 weeks, the beloranib group had a significantly greater mean reduction in hs-CRP compared with PBO (-13.7 vs -4.7 mg/L; p=0.009) and significant changes in adiponectin (+1.5 ug/mL) and leptin (-21.2 ng/mL) vs PBO (+0.3 ug/mL, p=0.036; -1.3 ng/mL, p=0.009; respectively). After 4 weeks the beloranib group had a significantly greater reduction in BW (-3.40 kg) vs PBO (-0.25 kg; p=0.01). Significant changes from baseline (p<0.05) were maintained during the 4-week extension for hs-CRP (-9.6 mg/L),

adiponectin (+1.8 ug/mL) and leptin (-25.4 ng/mL). Reduction in BW continued with beloranib treatment through Wk 8 (-6.2 kg). At Wk 8, significant improvements in total cholesterol (-20.6 mg/dL), LDL (-18.6 mg/dL), and triglycerides (-41.2 mg/dL) were observed with beloranib treatment ($p < 0.05$).

There were no serious adverse events and 1 adverse event leading to withdrawal (placebo; allergic reaction). All safety measures (laboratory, vital signs, ECGs) were unremarkable.

Conclusions: This Phase 2 proof of concept study demonstrated beloranib was safe and well tolerated in patients with HIAO and resulted in improvements in cardiometabolic profile and BW over 8 wks of treatment.

T-OR-2069

Intranasal Oxytocin Effects on Satiety Signaling and Sensory Perception in People with Schizophrenia

Kimberly Warren *Baltimore Maryland*, Robert Buchanan *Baltimore Maryland*, Robert McMahon *Catonsville MD*, Heidi Wehring *Baltimore MD*, AnnMarie Kearns *Brunswick MD*, Stephanie Feldman *Catonsville Maryland*, Deanna Kelly *Baltimore MD*

Background: Intranasal oxytocin has shown to play a role in appetite control in humans. Hence, intranasal oxytocin may be an effective treatment or preventative agent for obesity and weight gain in the schizophrenia population. Approximately 40-60% of people with schizophrenia are overweight or obese as compared with 30% of the general population.

Methods: The purpose of this study was to test a single dose of intranasal oxytocin (24 IU), compared to placebo, in a within-subjects, crossover design, to see if oxytocin would improve satiety signaling (behaviorally and/or by self report) compared to placebo in people with schizophrenia using a preload-test meal paradigm. Assessments of olfactory and gustatory functioning were also made.

Results: Eight males and eight females (N=16; 7 White, 7 Black, 2 other) between the ages of 22 and 56 (32±10.2) with a DSM-5 diagnosis of schizophrenia were included in the preload-test meal study. All 16 participants completed both conditions. Participants rated themselves (millimeters on a visual analogue scale (VAS)) as significantly less hungry when administered intranasal oxytocin (36.37±21.0) than placebo (44.81±28.6) 60 minutes following the consumption of the standardized preload (20 oz. vanilla Ensure®) ($F=8.05$, $df=15.5$, $p=0.012$). The total test meal intake did not differ between the conditions ($t=0.12$, $p=0.908$).

Conclusions: Intranasal oxytocin may be a promising agent in curbing appetite in people with schizophrenia or other populations. Further study is needed to test whether it may curb food consumption and help in weight loss.

T-OR-2070

Spatial Analysis of Childhood Obesity and Local Food Environment Inequalities in China

Hong Xue *Buffalo NY*, Peng Jia *Baton Rouge Louisiana*, Huijun Wang *BEIJING BEIJING*, Youfa Wang *Buffalo NY*

Background: Obesity prevalence in children increased rapidly over the past 30 years in China with large variations across groups. Limited is known how changes in local food environment (FE) have contributed to shifts of dietary intake and the temporal and spatial distributions of obesity in China.

Methods: The longitudinal China Health and Nutrition Survey data (1991 to 2011, covering 9 provinces) were used, where 190 communities with a total of 2,712 children in 1991 were included, and 171 of which remained followed up as of 2011. Local FE was measured by densities and approximates of a

wide array of food outlets within neighborhoods. Variations in FE over time and across province were examined. Fixed effects models and geographically weighted regression were used to explore the FE effects on obesity/overweight (obe/ovwt) in children in China.

Results: The northern provinces generally had a higher obe/ovwt rate and average BMI than southern provinces. The largest and smallest increases during 1991-2011 were found in Shandong province, from 19.3% to 40.8%, and Guangxi province, from 1.8% to 4.0%, respectively. The number of Chinese restaurants within neighborhoods increased from 1991 to 2000 and remained constant or increased in the majority provinces surveyed. The average numbers of both fixed and moving food stalls within neighborhoods rose before 2000, leveled off during 2000-2006, and then declined. The numbers of fixed and moving food stalls were positively associated with the obe/ovwt rates from 1991 to 2011 though the estimates were not statistically significant in some provinces. These associations also varied to different extents across provinces, stronger in northern provinces.

Conclusions: There were significantly unequal temporal and spatial changes of local food environment and obesity rates in China with varied patterns across region. The changes seemed to contribute to the increase and inequality of the obe/ovwt rates in Chinese children. Funding: NIH/NICHD (U54 HD070725-01)

T-OR-2071

Middle Eastern refugees are at high risk of developing obesity and chronic diseases in the U.S.

K-1. Catherine Jen *Detroit Michigan*, Hikmet Jamil *Detroit Michigan*, Kequan Zhou *Detroit mi*, Bengt Arnetz *Detroit MI*

Background: It is estimated that there are about 15.4 million refugees in the world and the U.S. admits more refugees for permanent resettlement than other countries. Many of these refugees experienced tremendous stress while in their homeland and developed post-traumatic stress disorders (PTSD). Many studies have reported high rate of mental and behavioral health disorders. Recent studies also showed that these refugees have high risk for developing chronic non-communicable diseases (NCD) and obesity.

Methods: In the present study, 298 newly arrived Iraqi refugees were followed-up for 2 years. Demographic, anthropometric, psychological and mental health data were collected within 2 month of resettlement (BL), at the end of years 1 (Y1) and 2 (Y2). Blood was also sampled from a subgroup of 60 refugees at the end of year 1. The retention rate at the end of Y2 was 95.9%.

Results: The body mass index (BMI) increased significantly and continuously (BL: 26.4±4.8 kg/m²; Y1: 26.92±4.8; Y2: 27.41±4.9, $p < 0.01$). There was an upward shift in BMI distribution over the years, more became obese and fewer were underweight. Refugees diagnosed with PTSD (yes/no) had significantly higher BMI than those without. Numbers of refugees with hypertension, type 2 diabetes or hypercholesterolemia also increased yearly. Total PTSD symptom scores were significantly correlated with BMI ($r=0.16$, $p=0.008$) and C-reactive protein ($r=0.49$, $p < 0.0001$). PTSD scores were significantly higher in refugees with diabetes or hypercholesterolemia than healthy refugees. Linear regression modeling revealed that BMI at Y2 was predicted by age, education, diabetes and PTSD scores.

Conclusions: Even though a causal relationship between PTSD and BMI or NCD cannot be established from this study,

strategies to reduce the symptoms of PTSD are warranted to help refugees maintaining a healthy BMI and reducing the risk of obesity and NCD.

T-OR-2072-Withdrawn

T-OR-2073

Racial Disparities in the Relationship between Severe Obesity, Income and Medicaid Coverage

Ashley Skinner *Chapel Hill North Carolina*, Stephen Cook *Rochester New York*

Background: Severe obesity is increasing in prevalence among children, yet coverage of evidence-based clinical treatment services limited, despite endorsement by USPSTF and requirement in the ACA. Our objective is to examine the relationships among severe obesity, insurance, and income, and differences by race, in a nationally-representative data set.

Methods: We examined children aged 3-19 in the National Health and Nutrition Examination Survey, 1999-2012 (n=22,214). We defined severe obesity as $\geq 120\%$ of the 95th percentile for BMI. Six categories of parent-reported income were: below Federal Poverty Level, up to >5 times the FPL. Parent-reported race categories were: non-Hispanic White, non-Hispanic Black, and Hispanic. We report prevalence of severe obesity by income and insurance. We used generalized linear models to examine effects of insurance and income on risk of severe obesity, and compared effect sizes by race using simultaneous models.

Results: Children in households below poverty (vs. above poverty), had a greater prevalence of severe obesity (5.6% vs. 3.4%, $p < 0.001$). Children with public insurance (vs. private) also had greater prevalence of severe obesity (7.7% vs. 4.2%, $p < 0.001$) GLM results showed a step-wise increase in the risk of severe obesity compared to highest-income children ($< 100\%$ FPL: aRR=2.9, 400-500% FPL: aRR=1.9, $p < 0.05$) and greater risk among those with public insurance (aRR=1.33, $p = 0.002$). In simultaneous models, the income difference persisted only for white children; public insurance was associated with increased risk among white and, to a lesser degree, Hispanic children.

Conclusions: Affluence only appears to provide a protective effect against severe obesity for white children. Prevention strategies, even in poor communities, are unlikely to reduce severe obesity. The high and disparate rates of severe obesity among the poorest household provides evidence that coverage of clinical treatment services is of an even greater need of those on public insurance.

T-OR-2075

Sex Differences in the Relation between Perceived Stress and Body Mass Index in a Nationally Representative Sample of Young Adults

Shakira Suglia *New York New York*, John Pamplin *New York New York*, Allana Forde *New York New York*, Rachel Shelton *New York New York*

Background: Perceived stress has been associated with increased risk of obesity, higher waist circumference and higher Body Mass Index (BMI), however sex differences have largely not been examined to date.

Methods: We examined the relationship between perceived stress and BMI and waist circumference in young adults in the National Longitudinal Study of Adolescent and Adult Health. During the wave 4 home visit, participants (mean age 29.0 n=14,283) completed the short form of Cohen's Perceived Stress Scale (PSS); responses were summed to create a PSS scale. Height, weight and waist circumference were assessed

during the same visit. BMI was calculated based on measured height and weight. Smoking status (current, former or never) and physical activity were assessed based on self-report during the wave 4 follow-up visit. To characterize socioeconomic status highest education level attained was characterized as less than high school, high school education, some college or completing a college degree or higher.

Results: In the sample, 50% were female and 67% identified as white. A sex by PSS interaction was noted ($p < 0.05$). In linear regression analyses adjusting for age, race/ethnicity, socioeconomic status, smoking status and physical activity, perceived stress was statistically significantly associated with lower BMI (B -0.10 SE 0.04) and lower waist circumference (B -0.20 SE 0.09) among men. No associations between perceived stress and BMI or waist circumference were noted among women.

Conclusions: In this nationally representative sample of young adults, sex differences are noted on the association between perceived stress and BMI. Contrary to previous findings perceived stress was associated with lower levels of adiposity among men. Future studies should examine differential coping strategies in response to stress between men and women as well as biological mechanisms that may explain the noted association.