glycosylated GPER in the ER. Inhibition of proteasome function facilitates anterograde trafficking with the transport of nonfunctional GPER to the plasma membrane as indicated by no increase in specific estrogen binding using ^{3}H-17β-estradiol in a radioreceptor assay. The forward trafficking of misfolded GPER requires transit through the Golgi as treatment with brefeldin A (BFA) prevents GPER plasma membrane expression. Substitution of all three lysines (K333, K342, and K357) encoded in the cytoplasmic tail of GPER with arginines blunts its polyubiquitinylation and allows GPER to evade degradation by quality control but does not result in increased plasma membrane expression suggesting that additional structural motifs encoded within GPER control its anterograde trafficking. In contrast, functional GPER is recovered at the plasma membrane of human SKBR3 breast cancer cells treated with either 17β-estradiol or the GPER selective antagonist, G15, in the presence of cycloheximide resulting in increased surface GPER. Thus, our findings suggest that estrogens, both natural and synthetic, can function as pharmacochaperones capable of promoting the correct folding of GPER and enhanced expression of functional GPER at the plasma membrane.

Adipose Tissue, Appetite, and Obesity
ADIPOSE TISSUE BIOLOGY AND OBESITY

Maternal Non-Nutritive Sweeteners Consumption Perturbs Development of Melanocortin Circuits Causing Long-Term Metabolic Alterations in the Offspring

Soyoung Park, PhD[1], Alice Jang, BA[1], Josephine Lowy, BA[1], Sebastien G. Bouret, PhD[2].
[1]University of Southern California, Los Angeles, CA, USA, [2]Inserm U1172, Lille, France.

SAT-LB104

Maternal Non-Nutritive Sweeteners Consumption Perturbs Development of Melanocortin Circuits Causing Long-Term Metabolic Alterations in the Offspring
Soyoung Park[1], Alice Jang[1], Josephine Lowy[1], Sebastien G Bouret[2] [1]Developmental Neuroscience & Diabetes and Obesity Programs, Children's Hospital Los Angeles, University of Southern California, Los Angeles, USA. [2] Inserm, Laboratory of Development and Plasticity of the Neuroendocrine Brain, Jean-Pierre Aubert Research Centre, UMR-S 1172, Lille, 59000, France.

With the growing prevalence of obesity and diabetes, including among pregnant women, non-nutritive sweeteners (NNS) have been widely used as an alternative to sugar in the attempt to deliver a sweet taste without excessive caloric load. However, there is little evidence regarding their biological effects particularly during critical periods of growth and development. In this study, we aimed to investigate whether maternal NNS consumption causes long-term neurodevelopmental and metabolic perturbations in the offspring. Adult female wild-type mice were exposed to either water (control), aspartame (0.03%), or rebaudioside A (0.02%) throughout pregnancy and lactation. Adult male, but not female, offspring from both aspartame- and rebaudioside A-exposed dams displayed increased adiposity and developed glucose intolerance. Moreover, maternal NNS consumption impaired pro-opiomelanocortin axonal projections to the paraventricular nucleus of the hypothalamus as well as reduced parasympathetic innervation of pancreatic islets. Taken together, our data indicate that maternal NNS consumption causes neurodevelopmental abnormalities in the offspring that may contribute to lifelong metabolic dysregulations.

Adipose Tissue, Appetite, and Obesity
ADIPOSE TISSUE BIOLOGY AND OBESITY II

Metabolic Inflexibility: Is It a Feature of Obesity or a Characteristic of Metabolically Unhealthy Youth?

Nour Y. Gebara, MD[1], Joon Young Kim, PhD[2], Fida Bacha, MD[3], SoJung Lee, PhD[4], Silva A. Arslanian, MD[1].
[1]UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA, [2]Syracuse University, Syracuse, NY, USA, [3]Baylor College of Medicine, Houston, TX, USA, [4]Kyung Hee University, Yongin, Korea, Republic of.

SUN-LB104

Obese individuals have metabolic inflexibility evidenced by diminished fasting fat oxidation and blunted increase in respiratory quotient (RQ) from fasting to insulin-stimulated state. Metabolically unhealthy obese (MUHO) adolescents, unlike their metabolically healthy obese (MHO) peers, have unfavorable metabolic characteristics despite having comparable adiposity. We investigated if metabolic inflexibility is a characteristic of obesity per se or is unique to MUHO compared with MHO youth.

Obese youth (n=188; age 14.1 ± 0.1 yrs [SE]; BMI 33.6 ± 0.4 kg/m^2) were divided into 137 MUHO (age 14.1 ± 0.2 yrs; BMI 35.4 ± 0.5 kg/m^2) and 51 MHO (age 13.9 ± 0.3 yrs; BMI 29.0 ± 0.7 kg/m^2) based on cut points for *in vivo* insulin sensitivity (IS) [MHO within 1.5 SD and MUHO <1.5 SDs of 72 normal-weight (NW) adolescents' IS values]. RQ (by indirect calorimetry) at fasting and during a hyperinsulinemic (80mu/m^2/min)-euglycemic clamp was measured, and ΔRQ calculated. Body composition (by DEXA), visceral adipose tissue (VAT) (by CT and MRI), hepatic IS (HIS) (calculated from fasting hepatic glucose production by [6,6-$^2H_2$]glucose and fasting insulin), adipose IS (ATIS) (calculated from whole body lipolysis by [$^2H_5$]glycerol and fasting insulin), and peripheral IS were assessed.

MUHO vs. MHO youth had blunted ΔRQ (0.088 ± 0.004 vs. 0.107 ± 0.007, p=0.035), but MHO was not different from NW (0.098 ± 0.004, p=0.893). Further, MUHO vs. MHO youth had lower HIS (15.3 ± 0.7 vs. 24.3 ± 1.6 (mg/kg/min·uU/mL)$^{-1}$, p<0.0001) and lower ATIS (9.8 ± 0.5 vs. 22.3 ± 3.1 (umol/kg/min·uU/mL)$^{-1}$, p<0.0001), but HIS and ATIS were not different between MHO and NW youth (24.3 ± 1.6 vs. 20.8 ± 1.2 (mg/kg/min·uU/mL)$^{-1}$, and 22.3 ± 3.1 vs. 22.0 ± 1.4 (umol/kg/min·uU/mL)$^{-1}$, p=ns for both). ΔRQ correlated with HIS (r=0.535), ATIS (r=0.288) and VAT (r=-0.309) (p<0.0001 for all), but not with BMI, BMI Z-scores or % body fat. The differences between MUHO and MHO youth in ΔRQ, HIS and ATIS remained significant after adjusting for % body fat, race, pubertal status and VAT.

The present study reveals that metabolic inflexibility is not a feature of obesity, rather it is a characteristic of MUHO youth who have significantly lower ΔRQ compared

with MHO youth, with no difference between MHO and NW youth. Moreover, MUHO compared with MHO youth have worse metabolic profile, represented in lower HIS and ATIS.

Tumor Biology

TUMOR BIOLOGY: DIAGNOSTICS, THERAPIES, ENDOCRINE NEOPLASIAS, AND HORMONE DEPENDENT TUMORS

Clinical Performance of Multiplatform Mutation Panel MicroRNA Risk Classifier in Indeterminate Thyroid Nodules

J. Woody Sistrunk, MD[1], Alexander Shifrin, MD[2], Marc Frager, MD[3], Ricardo H. Bardales, MD[4], Johnson Thomas, MD[5], Norman Fishman, MD[6], Philip Andrew Goldberg, MD[7], Richard B. Guttler, MD,FACE,FACP,ECNU[8], Edward Grant, MD[9].

[1]Jackson Thyroid & Endocrine Clinic, Jackson, MS, USA, [2]Hackensack Meridian Health Jersey Shore University Medical Center, Neptune, NJ, USA, [3]East Coast Medical Associates, Boca Raton, FL, USA, [4]Precision Pathology/Outpatient Pathology Associates, Sacramento, CA, USA, [5]Mercy Clinic Endocrinology, Springfield, MO, USA, [6]Diabetes & Endocrinology Specialists, Chesterfield, MO, USA, [7]Endocrine Associates of Connecticut, Branford, CT, USA, [8]Thyroid Center of Santa Monica, Santa Monica, CA, USA, [9]University of Southern California, Keck School of Medicine, Los Angeles, CA, USA.

SUN-LB24

Introduction: We evaluated the clinical performance of an expanded mutation panel in combination with microRNA classification (MPTX) for the management of indeterminate thyroid nodules. **Methods:** MPTX included testing of fine needle aspirates with a combination of ThyGeNEXT® mutation panel for strong and weak driver oncogenic changes and ThyraMIR® microRNA risk classifier. MPTX test status (positive or negative) and MPTX clinical risk classifications (low, moderate, or high risk) were determined blind to patient outcomes. Surgical pathology and clinical follow-up records of patients from multiple centers were used to determine patient outcomes. MPTX performance was assessed by Kaplan Meier analysis for cancer-free survival of patients, with risk of malignancy determined by hazard ratios (HR). **Results:** Our study included 140 patients with AUS/FLUS or FN/SFN nodules, of which 13% had malignancy. MPTX negative test status and MPTX low risk results conferred a high probability (94%) that patients would remain cancer free. MPTX positive test status (HR 11.2, P<0.001) and MPTX moderate risk results (HR 8.5, P=0.001) were significant risk factors for malignancy, each conferring a 53% probability of malignancy. MPTX high risk results elevated risk of malignancy even more so, conferring a 70% probability of malignancy (HR 38.5, P<0.001). **Conclusions:** MPTX test status accurately stratifies patients for risk of malignancy. Further classification using MPTX clinical risk categories enhances utility by accurately identifying patients at low, moderate, or high risk of malignancy at the low rate of malignancy encountered when clinically managing patients with indeterminate thyroid nodules.

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS III

Not That Sweet Honeymoon: A Case of Proinsulinoma.

Francisco Javier Lopez Maldonado, MD[1], Angel Alfonso Mayorga León, MD[1], Eduardo Rafael Leon Milan, MD[1], Carlos Alfonso Morales Chinchillas, MD[1], Jesus Alan Guardado, MD[2], Maria Elena Marin Fragoso, MD[1], Flor Maria Yocupicio, MD[1], Karla Itzel Luareano, MD[1], Alondra Rodríguez González, MD[2].

[1]Universidad Autónoma de Baja California, Facultad de Medicina, Mexicali, Mexico, [2]Centro de Estudios Universidad Xochicalco, Mexicali, Mexico.

SAT-LB314

Honeymoon Not So Sweet, A Case Of Proinsulinoma.

Introduction

Proinsulin-secreting tumors (proinsulinomas) are exceedingly rare, characterized by the predominant hypersecretion of proinsulin. We present an unusual case of hypoglycemic syndrome in a 19-year old woman with a proinsulinoma (PI).

Clinical Case

19-year-old female presented mild neuroglycopenic symptoms (SX) while having sexual intercourse with her husband at their honeymoon. Her condition began with diaphoresis, blurred vision, tremors and anxiety ending in somnolence that appeared exactly during sexual intercourse and disappear with orange juice intake. The SX kept appearing every time she had intercourse during the next month, denying that any other situation triggered them. She was referred to psychiatry where she was diagnosed with erotophobia and treated with fluoxetine and alprazolam. She gained 33 pounds and referred her husband gave her chocolate bars during sexual intercourse so SX wouldn't appear. 5 months later she presented cognitive deterioration characterized by stupor during intercourse, so she was taken to the emergency department (ED). Arrived the ED with tachycardia (110 bpm), BP 140/90 mmHg, stuporous, diaphoretic, pale and with a 27mg/dl blood glucose (BG). The patient was admitted to the hospital for further evaluation. After 12 hours of insulin fasting test, she began with SX and a 32 mg/dl glycometry was registered, the test was stopped afterwards. Serum labs were obtained: BG 28 mg/dl, insulin 3 (n 3.0-25.0Uiu/ML), C-peptide 0.9 (n 0.8-3.0ng/ml), proinsulin 298 (≤ 18.8 pmol/L). Abdominal CT scan in arterial phase revealed a single round, hypervascular image, located in the pancrea's body, 1.96 x 1.37 x 1.42 cm and 123 HU. Enucleation of the mass was performed. The histopathological report showed a neuroendocrine neoplasia and chromogranin positive immunohistochemistry in the neoplastic cells. Patient presented complete clinical remission, fluoxetine and alprazolam were discontinued and she lost 35 pounds in the next 6 months.

Conclusion

PI are predominantly benign neuroendocrine tumors that have the potential to cause symptomatic hypoglycemia. The patient's clinical manifestations were confused with an anxious syndrome and erotophobia, and these cases illustrate that the diagnosis of organic hypoglycemia can be challenging.