Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY

Central and Peripheral Endocannabinoid Levels in Obese Versus Lean Women

Mariana Farage-Martins, MFM, MD[1], Amelio Godoy-Matos, PhD[2], Denise Pires Carvalho, MD,DSc[3], Judith Harvey-White, PhD[4], Rosilene Taveira da Silva, PhD[5].

[1]Hospital de Fora Aerea do Galeao, Rio de Janeiro, Brazil, [2]IEDE, Rio de Janeiro, Brazil, [3]University Federal do Rio de Janeiro, Rio De Janeiro RJ, Brazil, [4]NIH, Bethesda, MD, USA, [5]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.

SAT-LB100

The endocannabinoid system (ECS) is thought to be involved in obesity because its activation increases appetite and weight gain (Pagotto et al 2006). The ECS is hyperactivated in the hypothalamus of obese mice, and peripheral overactivation has been observed in humans; circulating 2-arachidonoyl glycerol (2-AG) levels positively correlated with body fat, visceral fat and fasting glucose (Osei-Hyiaman et al 2005) (Bluher et al 2006) (Motaghedi and McGraw 2008) (Cavuoto et al 2007) (Artmann et al 2008) (Bermudez-Silva 2009). The aim of this study was to evaluate whether differential activation of the peripheral versus the central ECS occurred in humans and to test the hypothesis that the ECS is hyperactivated in the human central nervous system (CNS).Cerebral spinal fluid (CSF) and blood samples were collected from 13 obese and 11 lean control women to measure 2-AG and anandamide (AEA) levels. AEA levels were higher in the plasma of obese women (obese: 4.03 ± 0.91 pmol/mL, N=13; lean: 1.84 ± 0.21 pmol/mL, N=10; $p<0.05$) but were lower in the CSF of obese women. The plasma/CSF ratio was 41.58 ± 5.78 (N=10) in lean women and 103.0 ± 37.36 (N=6) in obese women (p=0.054). There were no correlations between plasma and CSF AEA levels or with any biochemical parameter. The 2-AG analysis was not possible because of technical problems.Our data suggested that in human obesity, the peripheral ECS may be more active than the central ECS. Indeed, the system appeared to be suppressed in the CNS of obese women. Therefore, the peripheral activation of the ECS may be more relevant for obesity. Keywords: Anandamide, 2-arachidonoyl glycerol, obesity, endocannabinoid, endocannabinoid system, cb1 receptor.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY

A Transcribed Ultraconserved Noncoding RNA, Uc.336-As, Promotes White to Brown Conversion in 3T3-L1 Cells

Xiaoying He, PhD, Tao Xiang, MA.Sc, Hongyu Guan, PhD, Yanbing Li, PhD.

The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

SAT-LB105

Brown adipose tissue (BAT) has gained its popularity since it shows great potential in counteracting obesity and metabolic diseases development. Transcribed ultraconserved regions (T-UCRs), a novel class of long noncoding RNA (lncRNAs), have been implicated in regulating diverse biological processes, including the process of white fat browning. However, the functional and mechanistic details of T-UCRs in the browning process are poorly understood. Here, we identified that a T-UCR, uc.336-as, played an important role during the browning process. Uc.336-as was significantly elevated during browning process induced by glucagon-like peptide-1 receptor agonist (exendin-4) or β3-adrenergic agonist (CL316,243). Overexpression of uc.336-as reduces the differentiation of 3T3-L1 preadipocytes into white adipocytes (inhibited lipid accumulation and decreased the expression of several adipogenesis markers) and induces brown characteristics during differentiation of 3T3-L1 preadipocytes (spurred browning adipocytes phenotypes and increased the expression of the browning associated genes). Moreover, we found that uc.336-as inhibited adipogenesis and promoted browning process via influencing the serine/threonine kinase (AKT)-mammalian target of rapamycin (mTOR) axis, an essential signal pathway in adipocyte metabolism. Taken together, our data show that uc.336-as acts as a negative regulator in white adipocyte differentiation and promotes the browning process, suggesting a potential therapeutic role for uc.336-as in controlling obesity.

Cardiovascular Endocrinology

ENDOCRINE HYPERTENSION AND ALDOSTERONE EXCESS II

Developing a Highly Equivalent Non-Competitive Chemiluminescence Immunoassay Aldosterone Measurement to LC/MS

Fumitoshi Satoh, MD, PhD[1], Yoshikiyo Ono, MD, PhD[2], Kei Omata, MD, PhD[2], Yuta Tezuka, MD and PhD[1], Hiroaki Yamanami, MD[1], Ryo Morimoto, MD, PhD[2], Satoshi Kojima, PhD[3], Hironobu Sasano, MD,PhD[1].

[1]Tohoku University Graduate School of Medicine, Sendai, Japan, [2]Tohoku University Hospital, Sendai, Japan, [3]Fujirebio Co. Ltd., Tokyo, Japan.

SUN-LB95

Background Measurement of plasma aldosterone and renin concentration, or activity, is useful for selecting antihypertensive agents anddetecting hyperaldosteronism in hypertensive patients. However, it takes several days to get results even if measured by inaccurateradioimmunoassay, or we must accept high-cost LC/MS, and development of a more rapid and accurate substitute has been long hoped. We havedeveloped a novel, fully-automated, high-quantitative noncompetitive chemiluminescence immunoassay (NC-CLEIA) for detecting aldosterone inserum and plasma, and its performance is evaluated as compared to LC/MS measurement. ***Methods*** Recently a unique anti-metatype antibody,which recognizes the immunocomplex of aldosterone and its monoclonal antibody, was established. Using this antibody for sensing permittedthe construction of non-competitive assay for the detection of aldosterone. The reaction protocol of novel aldosterone assay is the following. Inthe 1st reaction, aldosterone in patient's sample is captured on anti-body coated magnetic particles. Alkaline phosphatase-conjugated

antimetatypeantibody is added and incubated as 2nd reaction following a wash. Then substrate solution is added after washing immunocomplex.The resulting reaction signals are proportional to the amount of aldosterone in the sample allowing quantitative determination of in serum orplasma sample. The overall reaction is completed within 30 min. ***Results*** Limit of blank (LoB), limit of detection (LoD) and limit of quantitation(LoQ) of our NC-CLEIA aldosterone assay were 0.09 ng/dL, 0.21 ng/dL and 0.57 ng/dL, respectively. NC-CLEIA aldosterone measurements werelinearly well correlated with LC/MS aldosterone measurements (N = 130, y = 1.027x - 0.23 ng/dL, Spearman's ρ = 0.996, P< 0.0001). Bland-Altmanplot analysis between NC-CLEIA and LC-MS/MS of aldosterone revealed a bias of 0.40 ng/dL with the limits of agreement of -4.60 and 5.41 ng/dLwith 95% confidence interval. ***Conclusion*** Our novel NC-CLEIA aldosterone assay was well-correlated and had only a very low bias with LC-MS/MSmethod and also was able to accurately quantify low level samples even in essential hypertension patients. This aldosterone assay can be a most equivalent to LC-MS/MS measurement with a low cost of 12 $ and a short measuring time of 30 minutes.

Pediatric Endocrinology

PEDIATRIC OBESITY, THYROID, AND CANCER

Sporadic MTC in Children: Characterization of a Rare Disease

Sarah Gammons, MD[1], Mimi I. Hu, MD[2], Mark E. Zafereo, MD[2], Naifa L. Busaidy, MD[2], Nancy D. Perrier, MD[2], Roland L. Bassett, MS[2], Samuel M. Hyde, MMSc[2], Elizabeth G. Grubbs, MD[2], Steven G. Waguespack, MD[2].

[1]Baylor College of Medicine, Houston, TX, USA, [2]University of Texas MD Anderson Cancer Center, Houston, TX, USA.

MON-LB015

INTRODUCTION: Medullary thyroid carcinoma (MTC) is rare in children and is hereditary (hMTC), caused by germline mutations in the *RET* proto-oncogene, in about 95% of cases. Very little is known about sporadic MTC (sMTC) when diagnosed in children/young adults. Our aim was to study the clinical presentation and long-term outcomes of a large cohort of sMTC seen at a tertiary cancer center and to compare sMTC with hMTC in young patients (pts).

METHODS: Through a review of institutional databases, we identified pts diagnosed with MTC ≤ age 21 years (y.). Charts were retrospectively reviewed and data abstracted. The diagnosis of sMTC vs hMTC was determined based on germline *RET* testing and family history.

RESULTS: We identified 146 pts (53% female), of whom 20 (14%) had sMTC and 126 (86%) had hMTC (80 MEN2a and 46 MEN2b), with a median follow-up of 10 y. (range: 0.08-58, IQR 4.8-18). In pts with sMTC, the stage at diagnosis was I-II in 3/15 (20%) and stage III-IV in 12/15 (80%). Somatic mutations were identified in 11/12 tumors tested (6 *RET* p.M918T, 1 *RET* p.G691S, 2 *RET* deletions p.L629_L633del and p.E632_L633del, 1 *RET* c.2698_2710delinsC, and 1 *CCDC6-ALK* fusion). In contrast to hMTC, pts with sMTC were diagnosed at an older age [mean 18.0 y. ± 3.4 (range: 10-21) vs 12.9 y. ± 5.4 (range: 1.5-21), $p<0.001$], had higher calcitonin [median 889 (IQR 528-2634) vs 16 (IQR 3-117) x Upper Limit of Normal, $p<0.001$] and CEA levels [median 186 (IQR 46-468) vs 11 (IQR 4-16) x Upper Limit of Normal, $p<0.001$], larger tumors [median 2.5 cm (IQR 2-3.7) vs. 0.8 cm (IQR 0.4-1.9), $p<0.001$], and were more likely to be stage IV at diagnosis [73% vs 28%, $p<0.001$]. sMTC pts were less likely to have bilateral tumors [27% vs 81%, $p<0.001$] and, at last follow-up, had more persistent structural disease [79% vs 46%, $p=0.007$] and distant metastases [74% vs 37%, $p=0.005$]. Death from MTC occurred in 15% of pts with sMTC vs 6% pts with hMTC; median overall survival was not significantly different [30.6 y. in sMTC vs 39.3 y. in hMTC].

CONCLUSION: In this largest reported series of MTC in children/young adults, and the only study to look at sMTC in this population, we identified sMTC in 14% of MTC cases, a higher prevalence than is traditionally recognized but one that is possibly confounded by a referral bias. Somatic mutations were identified in 92% of samples tested, allowing for targeted therapy in those with distant metastases if needed. Compared with hMTC, patients with sMTC presented at an older age with higher tumor markers, larger tumors, and more unilateral disease. At last follow-up, persistent structural disease and distant metastases were more common in sMTC. The differences in clinical presentation and long-term outcomes likely reflect a variable path to MTC diagnosis. In conclusion, sMTC in pts ≤ age 21 y. presents at an older age with more advanced disease, frequently has an actionable driver mutation, and may be more common than previously thought.

Pediatric Endocrinology

PEDIATRIC GROWTH AND ADRENAL DISORDERS

Maintenance of Favorable Treatment Effect of Once-Weekly TransCon hGH for Children With Growth Hormone Deficiency: Interim Analysis From the Enlighten Long-Term Extension Trial

Aristides K. Maniatis, MD[1], Samuel J. Casella, MD, MSc[2], Ulhas M. Nadgir, MD[3], Gail J. Mick, MD[4], Paul Hofman, MD[5], Paul Saenger, MD[6], Elena D. Chertok, MD, PhD[7], Jeremy Warshauer, MD[8], Wenjie Song, PhD[8], Jessica M. Peng, PharmD[8], Allison S. Komirenko, PharmD[8], Aimee D. Shu, MD[8], Michael Beckert, MD[9], Elena M. Aghajanova, MD, PhD[10], Paul S. Thornton, MB BCh, MRCPI[11].

[1]Rocky Mountain Pediatric Endocrinology, PC, Centennial, CO, USA, [2]Dartmouth Hitchcock Medical Center, Lebanon, NH, USA, [3]Center of Excellence in Diabetes and Endocrinology, Sacramento, CA, USA, [4]University of Alabama Birmingham, Birmingham, AL, USA, [5]University of Auckland, Auckland, New Zealand, [6]NYU Langone Health, New York, NY, USA, [7]Voronezh State Medical University n.a. N.N.Burdenko, Voronezh, Russian Federation, [8]Ascendis Pharma, Inc., Palo Alto, CA, USA, [9]Ascendis Pharma, A/S, Hellerup, Denmark, [10]Yerevan State Medical University, Yerevan, Armenia, [11]Cook Children's Medical Center, Fort Worth, TX, USA.

SAT-LB16

Background Once-weekly TransCon hGH is an investigational long-acting prodrug for growth hormone deficiency (GHD) that consists of 3 components: unmodified growth hormone (hGH; somatropin), an inert carrier that protects it, and a linker that temporarily binds the two. In the