Healthcare Delivery and Education

EXPANDING CLINICAL CONSIDERATIONS FOR PATIENT TESTING AND CARE

Improving Thyroid Fine Needle Aspiration Education: Implementation of a Formal Clinical Procedure Assessment Tool for Teaching Thyroid FNA to Endocrinology Fellows

Priya Jaisinghani, MD[1], David A. Cohen, MD[2], Sara E. Lubitz, MD[3].

[1]Rutgers Robert Wood Johnson Medical School, Edison, NJ, USA, [2]Rutgers Robert Wood Johnson Medical School, Basking Ridge, NJ, USA, [3]Robert Wood Johnson Medical School, Westfield, NJ, USA.

MON-135

Fellows must demonstrate competence in the performance of thyroid biopsy (bx) from the 2019 ACGME Program Requirements for GME in Endocrinology, Diabetes, and Metabolism. During fellowship, trainees are often taught thyroid bx using an unstructured approach, through demonstration followed by supervised performance on patients. Concerns regarding patient safety, lack of readily available faculty & patients, and lack of competency checkpoints limit the utility of such an approach to teaching procedural skills [(1)]. Application of Psychomotor Learning Theory to teaching procedural skills has modified prior philosophy to "learn, see, practice, prove, do, maintain." [(2)] Two phases exist: 1) cognitive- conceptualization and visualization of the procedure and 2) psychomotor- acquisition of procedural skills. Formal training has been shown to improve FNA diagnostic accuracy along with fewer surgical procedures for benign lesions.[(2)] There is no evidence to support any specific recommendations for training fellows on safe and efficient thyroid bx techniques further highlighting the need for a competency based approach.[(3)] Since the didactic lecture format is not well suited for the acquisition of complex manual operations, in our study, we seek to 1) create, implement, and standardize the thyroid FNA curriculum for Endocrine fellows at our institution by employing global learning objectives and a skill checklist to help guide competency, and 2) assess the impact of this curriculum on knowledge, performance, and comfort. The goal is to prepare fellows for unsupervised practice through clinical procedure assessment tools to guide practical learning in conjunction with didactic lectures. Curriculum could be implemented not only across the nation to other endocrine fellowships but widely across multiple disciplines such as otolarynology, radiology, pathology. To assess the nationwide need for a formal means of teaching and evaluating thyroid US/ FNA skills within fellowship programs, we will be administering a nationwide survey to all Endocrinology Program Directors and recently graduated Endocrinology Fellows.

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Diabetes Mellitus and Glucose Metabolism

METABOLIC INTERACTIONS IN DIABETES

The Effect of Simvastatin on Glucose Metabolism in Primary Human Muscle Cells

Selina Mäkinen, MSci[1], Neeta Datta-Sengupta, PhD[1], Yen Nguyen, PhD[1], Petro Kyrylenko, MD[1], Markku Laakso, MD, Phd[2], Heikki A. Koistinen, MD,PhD[1].

[1]Helsinki University and Helsinki University Hospital, Helsinki, Finland, [2]UNIVERSITY OF KUOPIO, Kuopio, Finland.

SUN-657

Statin use, especially treatment with simvastatin, is associated with impaired insulin secretion and whole-body insulin sensitivity, and increased risk for T2D. Here, we investigated the direct effects of lactone- and acid-forms of simvastatin on glucose metabolism in primary human skeletal muscle cells. Exposure of human myotubes to lactone-form simvastatin for 48 h increased glucose uptake and glucose incorporation into glycogen, whereas the acid-form did not affect glucose uptake and decreased glucose incorporation into glycogen. These metabolic actions were accompanied by changes in insulin signaling, as phosphorylation of AS160 and GSK3β was upregulated with lactone-, but not with acid-form simvastatin. Exposure to both lactone and acid-forms of simvastatin led to a decrease in glycolysis and glycolytic capacity, as well as to a decrease in mitochondrial respiration and ATP production. Collectively these data indicate that lactone- and acid forms of simvastatin exhibit differences such that lactone-form increases, and acid-form impairs glucose incorporation into glycogen. Exposure to either form of simvastatin, however, impairs glycolysis and mitochondrial oxidative metabolism in human skeletal muscle cells.

Diabetes Mellitus and Glucose Metabolism

CLINICAL AND TRANSLATIONAL STUDIES IN DIABETES

DREADD-Induced POMC^{ARC}Neuron Activation Increases Fasting Plasma Glucose Levels Through Changes in Hepatic Gluconeogenic Gene Expression but Not Changes in the HPA Axis Activity.

Luane da Guia Vieira, master's degree student[1], Alan Carlos Fernandes, Biologist[1], Tais Nascimento, undergraduate student[1], Suzelei de Castro França, PhD[1], Jose Antunes-Rodrigues, MD,PhD[2], Kristen R. Vella, PHD[3], Lucila Elias, MD,PHD[4], Rodrigo Rorato, PHD[1].

[1]University of Ribeirao Preto - UNAERP, Ribeirao Preto, Brazil, [2]School of Medicine of Ribeirao Preto, Ribeirao Preto SP, Brazil, [3]Weill Cornell Medicine, New York, NY, USA, [4]School of Medicine of Ribeirao Preto, Ribeirao Preto, Brazil.

MON-637

POMC neurons expressed in the ARC are essential for energy balance and glucose homeostasis. It has been suggested the involvement of these neurons in the control of endocrine axes, such as the HPA. During fasting, $POMC^{ARC}$ neurons are silenced as an effort to reduce body weight loss and to avoid hypoglycemia. During this process glucocorticoid secretion and activation of enzymes involved in the hepatic gluconeogenesis take place in order to preserve the homeostasis. In this study, to clarify the contribution of $POMC^{ARC}$ neurons to the adaptive changes in energy homeostasis, glucose metabolism and HPA axis activity induced by food deprivation we used DREADDs to specifically activate $POMC^{ARC}$. Bilateral injections of the AAV carrying the excitatory DREADD (hM3DGq) or only the reporter gene (mCherry) have been performed into the ARC of *Pomc-ires-cre* and WT mice. Two weeks later the animals were fasted for 36hr, treated with saline (5 i.p. injections each 8hrs) and blood samples were collected from the facial vein at 10am. Two weeks apart, the same animals were submitted to another period of fasting and treated with CNO (1mg/Kg, 5 i.p. injections each 8hrs). Four hours after the last injection of CNO, the mice were anesthetized, blood and the liver were collected and then the animals perfused for brain harvesting. Body weight measurements have been performed before and after the 36hrs period of fasting. Another set of *Pomc-ires-cre* (hM3DGq or mCherry) and WT animals were fasted (36hrs), treated with CNO (5X) and subjected to GTT. DREADD–induced activation of $POMC^{ARC}$ neurons has been confirmed by the increased cFos/mCherry expression after CNO treatment only in *Pomc-ires-cre* animals expressing hM3DGq. We observed that the specific activation of $POMC^{ARC}$ neurons did not change the fasting-induced activation of HPA axis. Surprisingly, we observed reduced body weight loss and higher plasma glucose in *Pomc-ires-cre* animals expressing the hM3DGq and treated with CNO. The GTT showed an impaired glucose tolerance after activation of $POMC^{ARC}$ neurons. The increased fasting glucose plasma levels was associated with increased *G6pc* (Glucose-6-phosphatase) mRNA expression but with no effect on other hepatic gluconeogenic genes. The present study reveals that $POMC^{ARC}$ neurons are not involved in the increased HPA axis activity in prolonged fasting conditions. Considering the classical anorexigenic/thermogenic and the glucose-lowering action of $POMC^{ARC}$ neurons, the present data reveal an unpredicted reduced body weight loss and impaired glucose tolerance induced by activation of these neurons during fasting. These data reinforce the notion that $POMC^{ARC}$ neurons are heterogeneous and might be playing dual effects on energy homeostasis. Of note, because part of ARC neurons shares a common progenitor, some of the functions ascribed to POMC neurons could be mediated by non-POMC neurons expressing the Cre transgene.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING I

Association of Single Nucleotide Polymorphisms of CYP11B2, CYP11B1 and CYP17A1 with Primary Aldosteronism in a Multi-Ethnic Malaysian Cohort

Afifah Azam, BSc[1], Mohammad Arif Shahar, MD[2], Siti Liyana Saud Gany, BSc[1], Norlela Sukor, PhD[3], Nor Azmi Kamaruddin, MBBS,MMED, FACE[1], Scott Mackay MacKenzie, BSc(Hons),PhD[4], Elena Aisha Azizan, Dr, PhD[1].

[1]National University of Malaysia (UKM) Medical Centre, Kuala Lumpur, Malaysia, [2]International Islamic University Malaysia, Kuala Lumpur, Malaysia, [3]National University of Malaysia (UKM) Medical Centre, Kuala Lampur, Malaysia, [4]University of Glasgow, Glasgow, United Kingdom.

SUN-711

Abstract: Primary aldosteronism (PA), also known as Conn's syndrome, is a common curable cause of hypertension. Family studies of essential hypertensive patients suggest that heritable genetic factors play a role in blood pressure regulation[1]. Interestingly, single nucleotide polymorphisms (SNP) in genes encoding enzymes involved with adrenal steroidogenesis, *CYP11B2*, *CYP11B1* and *CYP17A1*, associate with increased risk of hypertension[2]. Therefore, we analysed whether selected SNPs in these genes are associated with PA. We performed an association study using genotype imputation for selected SNPs of the steroidogenic enzyme genes *CYP11B2* (rs4546, rs1799998, rs13268025), *CYP11B1* (rs6410, rs149845727), and *CYP17A1* (rs1004467, rs138009835, rs2150927) from a pilot genome wide association study of Malaysian PA patients and healthy controls which was merged with the Singapore Genome Variation Project (SGVP) population dataset[3]. Genotype imputation for minor and major alleles was validated using PCR sequencing (n>10 for each genotype). Further, one SNP from each steroidogenic enzyme (*CYP11B2*:rs1799998, *CYP11B1*:rs6410 and *CYP17A1*:rs1004467) was validated using commercial TaqMan genotyping assays on the ABI 7000 Sequence Detection System which was performed on 149 PA patients and 78 non-hypertensive healthy individuals. Case-control genetic association analysis was performed at http://www.oege.org/software/orcalc.html and the association between genotypes and phenotypes was done using the independent-samples Kruskal-Wallis test on SPSS (version 25). The Minor Allele Frequencies (MAFs) for rs1004467, rs6410 and rs1799998 were similar to East Asian populations but differed significantly different from European, African, American and South Asian populations (rs1004467 MAF: C=0.258/298, rs6410 MAF: A=0.265/298, rs1799998 MAF: C=0.225/298). In Chinese patients matched by gender, heterozygotes for rs6410 had significantly increased risk of PA compared to common homozygotes (OR: 3.15, 95% CI: 1.01–9.8, p=0.04). Across patients of different ethnicity, the distribution of aldosterone levels was significantly different (p=0.039). In summary, only SNP rs6410 in Chinese patients matched by gender showed association with PA in our South East Asian cohort. More functional experiments need to be done to find out whether this is causal for PA or whether the SNP is in linkage disequilibrium with the actual functional causative SNPs. Once the functional SNP is known, identification of these germline variants in asymptomatic family members would allow early screening of PA to be offered and potentially provide novel drug targets to treat the disease.

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