

group (70.0% vs. 35.5%, $P < 0.001$). In the subscale results, stimulus values in 2000 Hz, hypoesthesia and hyperesthesia were significantly higher in the poor sleep quality group, than in the good sleep quality group (45.7% vs. 25.0%, $P = 0.009$; 34.3% vs. 18.4%, $P = 0.029$; 40.0% vs. 19.7%, $P = 0.007$, respectively). The association of painless DPN and poor sleep quality remained significant after adjustment for significant variants (odds ratio, 3.825; 95% confidence interval, 1.674-8.742; $P < 0.001$).

Conclusions

The current study showed that painless DPN was associated with poor sleep quality. Future studies are required to clarify the pathophysiologic causal relationship between painless DPN and sleep quality.

References

- Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai K-S, Stacey B. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. *Journal of pain and symptom management*. 2005;30(4): 374-385.
- Zelman DC, Brandenburg NA, Gore M. Sleep impairment in patients with painful diabetic peripheral neuropathy. *Clin J Pain*. 2006;22(8): 681-685.

Pediatric Endocrinology

PEDIATRIC PUBERTY, TRANSGENDER HEALTH, AND GENERAL ENDOCRINE

Urine Steroid Profile of Girls with Premature Adrenarche

Grit Sommer, PhD¹, Marco Janner, MD¹, Michael Groessl, PD, PhD², Christa E. Flueck, MD¹.

¹Bern University Children's Hospital, Inselspital, Bern, Switzerland, ²University Hospital Bern, Inselspital, Bern, Switzerland.

SUN-073

Background: Adrenarche describes the development of the human adrenal cortex when the zona reticularis increases the synthesis of C19 steroids (DHEA/S). Girls with premature adrenarche have a higher risk to develop adverse outcomes including polycystic ovary syndrome and metabolic syndrome later in life. The role of novel biosynthetic pathways of androgen production in health and disease remains largely unsolved.

Objective: This study aimed to compare the urinary steroid metabolome between girls with premature adrenarche and healthy girls with focus on metabolites originating of novel, alternate androgen pathways.

Methods: In 23 girls with premature adrenarche (median age 7 years) and 22 healthy, age-matched girls, we measured 39 steroid metabolites comprising progesterones, corticosterones, aldosterone, androgens, estrogens and glucocorticoids in the urine collected over 24 h by gas chromatography mass spectrometry. We compared metabolites and metabolite ratios between both groups of girls using Mann-Whitney tests with Bonferroni correction to account for multiple testing.

Results: Girls with premature adrenarche were heavier than healthy girls (median weight 26.2 kg vs. 21.5 kg, $p = 0.003$) and had a higher BMI SDS (0.8 vs -0.3, $p = 0.013$). Gestational age and birth weight was similar between

groups. Overall androgen excretion was different between groups, in particular amounts of androsterone, etiocholanolone, androstanediol, dehydroepiandrosterone, androstenediol, androstenetriol and pregnenetriol were higher in girls with premature adrenarche than in healthy girls ($p < 0.05$). Some of these metabolites originate from alternate androgen pathways, e.g. androsterone. We found no differences in progesterones, corticosterones, aldosterone, estrogens and glucocorticoids, except for 20 β -dihydrocortisone, which was higher in girls with premature adrenarche. Activities of 17 β HSD and of 17,20-lyase via the $\Delta 4$ pathway were higher in girls with premature adrenarche than in healthy girls.

Conclusions: Girls with premature adrenarche produce more androgens than healthy girls of similar age. The urinary steroid signature of adrenarche includes metabolites of alternate pathways. Androstanediol seems a marker of adrenarche. Future studies should assess whether the steroid signature of adrenarche is just appearing earlier in girls with premature adrenarche or earlier and different compared to adrenarche at normal timing.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY

Cold-Acclimation Prevents the Onset of Glucocorticoid-Induced Adipose Dysfunction in Male Mice

Manuel M. Gado, MSc¹, Monique Noll, MSc¹, Annett Heinrich, BSc¹, Martina Rauner, PhD², Lorenz C. Hofbauer, MD², Holger Henneicke, MD, PhD¹.

¹Center for Regenerative Therapies TU Dresden, Dresden, Germany, ²Technische Universität Dresden Medical Center, Dresden, Germany.

SAT-586

Glucocorticoid (GC) excess, either endogenously or exogenously, has been causally linked to the development of chronic diseases such as obesity and type-2 diabetes mellitus. Continuously elevated GC levels result in an expansion of white adipose tissue (WAT) depots and a dramatic decrease in the thermogenic capacity in brown and beige adipose tissue (BAT and BeAT, respectively). Herein we aimed to examine the interaction between GCs and the sympathetic nervous system (SNS) in the regulation of WAT, BAT, and BeAT. To this end, we utilized an altered environmental temperature as a non-invasive method for the modulation of sympathetic activity - cold is an activator of SNS-mediated non-shivering thermogenesis. Thus, during a 4-week treatment with either corticosterone or placebo, 10-week-old male C57BL/6NRj mice were maintained at two different temperature levels: 29°C (thermoneutrality) or 13°C (cold temperature). Body weight, as well as energy and water intake, were monitored throughout the study. At sacrifice, serum and adipose tissues were collected for analysis. GC-exposed mice showed a marked increase in circulating corticosterone concentrations compared to placebo controls with no appreciable difference between temperature levels. At thermoneutrality, GC-treated mice gained more weight and consumed more food than their placebo-treated littermates. This GC-induced body weight gain was accompanied by increased (visceral & subcutaneous) WAT

weight as well as adipocyte hypertrophy. Interestingly, cold-acclimatized mice showed a marked reduction in GC-induced weight gain, hyperphagia, and fat accumulation. Moreover, the GC-induced rise in blood glucose and serum insulin concentrations - readily observed when mice were maintained at thermoneutrality - was absent in cold-exposed animals. In addition, GC treatment at thermoneutrality resulted in increased lipid deposition and decreased UCP1 expression in BAT, the 'whitening' of BAT. This GC-induced loss of thermogenic capacity was profoundly reduced in cold-adapted mice. Across all groups, UCP-1 protein levels in BAT closely correlated ($r^2 = 0.70$, $p < 0.0001$) with those of tyrosine hydroxylase (TH), the rate-limiting enzyme of catecholamine synthesis. These results indicate that cold-acclimation prevents the development of GC-induced metabolic dysfunction in mice. Thus, environmental temperature is a potent modulator of GC-induced adiposity and body weight gain, potentially via an interaction between SNS and GC signaling.

Steroid Hormones and Receptors

STERIOD BIOLOGY AND ACTION

Expression of SLC35F1 in the Plasma Membrane of Cells of Aldosterone Producing Cell Clusters (APCCs) and Its Possible Role in Aldosterone Synthesis

Emily Goodchild, BMBS, BSc, MRCP¹, Jan Stoetaert, BSc, PhD, ir¹, William Drake, DM, MRCP², Kenneth Linton, BSc, PhD¹, Morris Jonathan Brown, MD, FRCP³.

¹Queen Mary University London, London, United Kingdom,

²Saint Bartholomew's Hosp, London, United Kingdom, ³Queen Mary University of London, London, United Kingdom.

OR09-05

Background Genetic mutations and histological appearances suggest that APCCs are precursors to some aldosterone producing adenomas (APA). They are hypothesised to contribute to post-operative non-cure and recurrence of primary aldosteronism (PA) but are currently undetectable pre-operatively. SLC35F1 is a possible nucleotide sugar transporter. On microarray it is highly expressed in APCCs, but not in the rest of the adrenal cortex (1). Our aim was to investigate the role of SLC35F1 in APCCs, determine its subcellular localisation and establish whether expression is consistent with pathological APCC subtypes (as suggested by recent evidence from *in situ* metabolomic studies (2)). **Methods** Comparative bioinformatic analysis of the SLC35F1 amino acid sequence was carried out. *Ex vivo* 4uM adrenal sections, from 6 PA patients in the MATCH study, were stained on serial sections with anti-CYP11B2 (Gomez-Sanchez) or anti-SLC35F1 (Novus NBP1-86755). *In vitro*, H295R cells were transfected with SLC35F1 cDNA. Subcellular localisation of SLC35F1-GFP was studied by comparison to organelle markers (golgin 97, RAB11, wheat germ agglutinin, calnexin and Tom20) using confocal microscopy. Overexpression and siRNA knock-down in H295R cells was correlated to aldosterone production. **Results** SLC35F1 is a decamembrane-spanning transporter molecule predicted to have a negatively charged pocket in the substrate binding site, implying a transport substrate with a positive charge. Strong staining of CYP11B2 in clusters of cells in adrenal cortex, consistent

with APCCs, were present in all six adrenal glands (25 APCCs). Serial sections showed specific SLC35F1 staining of APCCs, in cytoplasm and plasma membrane. SLC35F1 staining was absent from normal cortex. 12 APCCs (48%) were SLC35F1-negative. Visualisation of transiently expressed SLC35F1 demonstrated localisation to the endoplasmic reticulum in H295R cells (Pearson's coefficient $r=0.758$) with no plasma membrane localisation ($r=-0.07$). Preliminary transfection data suggest direct involvement in aldosterone production. **Conclusions** Expression of SLC35F1 in the plasma membrane and cytosol of APCC cells supports a role in pathological aldosterone production by APCCs. The inferred transport substrate of SLC35F1 is the NAD(P)(H) precursor, nicotinamide riboside, a positively-charged nucleotide sugar. If confirmed, the essential requirement for NAD(P)H in steroidogenesis, and heterogeneity of SLC35F1-staining in APCCs, is consistent with a metabolically active, possibly pathological, subtype of APCCs. Detection of SLC35F1 *in vivo* may therefore facilitate sub-classification of PA patients.

- 1). Nishimoto et. al. PNAS. 2015 Aug 18;112(33):E4591-9.
- 2). Murakami et. al. 2019 Hypertension. In press.

Diabetes Mellitus and Glucose Metabolism

TYPE 1 DIABETES MELLITUS

The Lesser Evil: Pembrolizumab Induced Remission of Metastatic Melanoma with Autoimmune Diabetes, Hypothyroidism, and Colitis

Asaf Harris, MD¹, Kayla Andres, MD², Mohammad Kawji, MD¹.

¹Spectrum Health / Michigan State University, Grand Rapids, MI, USA, ²Mercy Health Saint Mary's, Grand Rapids, MI, USA.

SAT-661

Background: Immune checkpoint inhibitors (ICI) are a new class of immunotherapy agents that empower the innate immune system to destroy cancer cells by overcoming checkpoints against autoimmunity and self-tolerance. ICI use against certain cancers has yielded impressive results. Pembrolizumab, an ICI approved by the FDA in 2014 for treatment of metastatic melanoma, is a monoclonal antibody which binds the programmed cell death protein 1 (PD1) receptor, blocking its activation. Recent case reports have demonstrated a link between pembrolizumab and severe immunotherapy related adverse events including the incidence of autoimmune disorders.

Clinical Case: A 68-year-old male with hypertension and a past medical history of cutaneous melanoma treated fifteen years earlier with tumor resection was started on pembrolizumab after identification of new metastases to the lung and bones. After 3 cycles of therapy he began to experience dizziness, lightheadedness, and vision changes with diarrhea. Outpatient labs demonstrated hyperkalemia with hyponatremia. He was directed to the emergency department by his oncologist for presumed adrenal insufficiency, where he received one dose of IV dexamethasone (4 mg). Repeat labs demonstrated severe diabetic ketoacidosis with elevated blood glucose 981 (70-99 mg/dL), pH 7.19 (7.32-7.42), anion gap of 37 (4-15 mmol/L), and betahydroxybutyrate > 9.00 (0.00-0.40 mmol/L). Following endocrinology consultation steroids were discontinued