parameters in 38 subjects with LD (18 GLD, 20 PLD) who were treated with metreleptin in open-label clinical studies at the National Institutes of Health. 27 had repeat echo after 1y of metreleptin (mean 1.0 ± 0.2y), and 23 after 3 to 5y (mean 3.7±0.6y). In GLD, metreleptin significantly improved metabolic disease, including reduced TG (median(IQR) 740(403–1239), 138(88–196), 211(136–558) mg/dL at baseline, 1y, & 3-5y, P<0.0001), hemoglobin A1c (9.5±3.0, 6.5±1.6, 6.5±1.9% at baseline, 1y, & 3-5y, P<0.001), and insulin resistance by HOMA-IR (34.1 (15.2–43.5), 8.7 (2.4–16.0), 8.9 (2.1–16.4), P<0.001). Only HOMA-IR improved in PLD (P<0.01). Systolic BP and HR decreased after metreleptin in GLD (BP 120±11, 117±10, 109±16 mmHg, P=0.046; HR 89±9, 82±12, 80±16 bpm, P=0.018; at baseline, 1y, 3-5y, respectively) but not PLD. Metreleptin improved cardiac parameters in patients with GLD, including reduced posterior wall thickness (9.8±1.7, 9.1±1.3, 8.3±1.7 at baseline, 1y, & 3-5y, P<0.01), LV mass (140.7±45.9, 128.7±37.9, 110.9±29.1 at baseline, 1y, & 3-5y, P<0.01), and LV mass index (88.6±22.0, 81.6±16.9, 81.6±16.9 at baseline, 1y, & 3-5y, P<0.01). Metreleptin also improved septal e' velocity, a measure of early diastolic cardiac function, in GLD (8.6±1.7, 10.0±2.1, 10.7±2.4 at baseline, 1y, & 3-5y, P<0.01). All changes remained significant after adjustment for BP. In GLD, multivariate variable selection models suggested that changes in posterior wall thickness and LV mass index related to metreleptin-induced reductions in TG, and changes in septal e' velocity related to metreleptin-induced reductions in hemoglobin A1c. No changes in echo parameters were seen in PLD. These findings suggest that metreleptin improves cardiac hypertrophy and diastolic function in patients with GLD, and these improvements may be mediated by reduced lipotoxicity and glucose toxicity. The applicability of these findings to a broader, leptin-sufficient population with LV hypertrophy and/or diabetic cardiomyopathy remains to be determined.

Cardiovascular Endocrinology

LIPIDS AND STEROIDS IN CARDIOVASCULAR DISEASE

The Impact of ACTH on Peripheral Steroids Differs between Unilateral and Bilateral Primary Aldosteronism

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Background: ACTH is thought to contribute to aldosterone excess in primary aldosteronism (PA), possibly via aberrant melanocortin type 2 receptor (MC2R) expression in aldosterone producing adenomas (APAs). Dynamic manipulation of the hypothalamic-pituitary-adrenal (HPA) axis has been proposed as a non-invasive tool for distinguishing unilateral PA (UPA) from bilateral PA (BPA), but existing data are minimal. **Objective:** To characterize the steroid responses to intrinsic ACTH variations and extrinsic HPA manipulation in UPA and BPA. **Methods:** We conducted comprehensive dynamic testing in PA patients, who were subtyped based on adrenal vein sampling. Peripheral plasma samples were collected from each patient at 6 time-points: morning; midnight; after 1 mg dexamethasone suppression (DST); and after cosyntropin stimulation (at 15', 30', and 60'). We quantified 15 steroids by mass spectrometry in each sample. Next generation sequencing was used to detect aldosterone-driver somatic mutations in APAs from 39 cases with available tissue. The Mann-Whitney test, Wilcoxon signed rank test, and repeated measures two-way ANOVA were employed, as appropriate. Penalized logistic regression was used to select steroids that best distinguished UPA from BPA. Receiver operating characteristic (ROC) curves were then plotted using the predicted score from the logistic regression model with the selected steroids, and area under the curves (AUC) were computed. **Results:** We included 80 PA patients, median age 51 (range, 26–76), 50% men, 40 with each subtype, both groups with similar age and sex distribution. Morning and midnight concentrations of 18-hydroxycortisol (18OHF), 18-oxocortisol (18oxoF), aldosterone, and 18-hydroxycorticosterone (18OHB) were higher in patients with UPA vs. BPA (p<0.001 for all). In response to cosyntropin stimulation, the UPA group had larger increments of aldosterone, 18oxoF, 11-deoxycorticosterone, corticosterone, and 11-deoxycortisol than the BPA group (p<0.05 for all). Following DST, aldosterone,18OHF, and 18oxoF were higher in UPA than in BPA patients (p<0.01 for all). Overall, cortisol and cortisone serum concentrations were similar between the two subtypes. Of the UPA cases, 27 (69%) had *KCNJ5* mutations. Relative to UPA patients with other mutations, the *KCNJ5* group had higher 18oxoF and 18OHF at baseline; higher 18oxoF and corticosterone after both dynamic tests; and lower aldosterone after DST. The highest AUC for PA subtyping was achieved using cosyntropin stimulated steroids (0.957), while baseline data reached an AUC of 0.909. **Conclusions:** Steroid responses to dynamic HPA testing differs between UPA and BPA: 18oxoF and 18OHF are less suppressible, while several steroids are disproportionally amplified by ACTH in patients with UPA vs. BPA. Such non-invasive tests could circumvent the need for adrenal vein sampling in a subset of PA patients.

Diabetes Mellitus and Glucose Metabolism

BENCH TO BEDSIDE: NOVEL MECHANISMS IN DIABETES AND METABOLISM

Analysis of Novel Histone Methylase MLL Function for Glucose Metabolism in Mouse Pancreas

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Background) Myeloid / Lymphoid or Mixed-lineage leukemia gene (MLL) is translocated to chromosome 11 long arm q23 region (11q23) and the MLL fusion gene expressed as a result of translocation reconstruction plays an important role in MLL-related leukemia development. It has also been reported that MLL and MLL protein play an important role in tumor development as a Menin-binding protein in Multiple Endocrine Neoplasia Type I (MEN1). More recently, normal MLL protein has been shown to have histone H3 lysine 4-methylation (H3K4-HMT) activity and to be an epigenetic transcriptional regulator. In addition, the function of MLL protein as a histone methylase has been reported in the gene region involved in metabolism regions. Here, we analyzed the involvement of MLL in glucose metabolism in the pancreas using MLL knockout mice. **Methods:**) Glucose metabolism in MLL knockout mice and the function of MLL in cultured cells were analyzed. Result) Since the homozygotes of MLL knockout mice are embryonic lethal, we analyzed them using Heterozygous mice. MLL heterozygous mice showed significantly weight loss compared to the wild type mice. MLL heterozygous mice showed no difference in food intake compared to wild type mice. IPGTT showed impaired glucose tolerance in MLL heterozygous mice. However, ITT showed no insulin resistance and decreased insulin secretion during glucose loading. In GSIS tests, Islets isolated from heterozygous mice pancreas have been observed to decrease insulin secretion in the response to glucose stimulation. In comprehensive gene analysis using Microarray analysis of mRNA extracted from mice islet, the gene expression changes related insulin secretion and apoptosis have been revealed in MLL heterozygous mice. Histological search showed no decrease in β-cell number, and immunohistological search showed no difference in insulin, glucagon, and TUNEL staining between heterozygous and wild type mice. And also, MLL knockdown was performed in a cultured cell line. Insulin secretion was decreased to glucose stimulation in MLL knockdown cell line same as in MLL knockout mice. In addition, RNA microarrays were performed to these cell lines, several same genes that have confirmed in MLL mouse islets were observed in MLL knockdown cell. In conclusion, MLL knockout mice showed decreased insulin secretion. It was suggested that MLL may be involved in insulin secretion in islets.

Diabetes Mellitus and Glucose Metabolism

BENCH TO BEDSIDE: NOVEL MECHANISMS IN DIABETES AND METABOLISM

Antidiabetic Effects of NRDT50, the Enzyme Composition for Regulating Sugar Metabolism, in Db/db Mice

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Objective: The enzyme composition (NRDT50) which includes glucosyl transferase, fructosyl transferase, amylase, glucose oxidase, and catalase can regulate the absorption of glucose into the body by converting the carbohydrates in food to a form of sugar that is not absorbed in the stomach before being decomposed in the small intestine into glucose. The aim of this study was to evaluate the antidiabetic effects of repeated oral administration of NRDT50 in db/db mice. **Methods:** The 7-week-old db/db mice were divided into 3 groups; control, NRDT50 (300mg/kg/day), and voglibose (0.3mg/kg/day). Mice received a standard diet containing drugs for 1 month. Fasting and postprandial glucose level was measured every week. Mixed meal test, biochemical assays, and fecal microbiota analysis were performed. **Results:** There were no significant differences in body weight or food intake between the three groups. However, NRDT50 treatment led to a significant reduction in fasting and postprandial blood glucose levels compared to control after 3, 4 weeks. The blood glucose levels during the mixed meal test were significantly lower in NRDT50 group compared to control group. NRDT50 treatment reduced triglyceride level, tend to reduce LDL level, and increased relative Bacteroidetes-Firmicutes ratio. NRDT50 treatment did not demonstrate any negative side effects on biochemical and histopathological examination. Conclusion: NRDT50 is expected to be useful for people who are at risk of hyperglycemia or diabetes and thus need to regulate blood sugar with safe. It may also improve the gut microbiota profile by inducing the production of oligosaccharides in the alimentary tract.