Group D, Controls (19 patients, 13 F and 6 M, mean±SEM age 40.26±2.87 ys, BMI 23.25±0.95 kg/m^2). The diagnosis of metabolic syndrome was made according to NCEP ATPIII criteria (2005 revision). GHD was diagnosed with dynamic test using Growth Hormone-Releasing Hormone (GHRH 50 μg i.v. + arginine 0,5 g/Kg), with a peak GH response between 9 and 16 μg/L when BMI was < 30 kg/m^2 or 4 and 9 μg/L when BMI was > 30 kg/m^2. Partial GHD was defined with dynamic test using GHRH, with a peak GH response < 9 μg/L when BMI was < 30 kg/m^2 or < 4 μg/L when BMI was > 30 kg/m^2.They were evaluated for: serum glucose and insulin, HOMA-index, QUICKI-index, Total/LDL/HDL cholesterol, triglycerides, IGF-1 and LCN2 (measured using ELISA kit DuoSet LCN2/NGAL, R&D systems).LCN2 plasmatic levels were significantly increased in METs, while no difference with control group was found in total and partial GHD. LCN2 levels were not influenced by BMI and HOMA-index. A significant positive correlation between LCN2 and HOMA-index was found in controls, while a trend-like, yet not significant, positive correlation was evidenced in partial GHD. No correlations between these parameters were identified in METs and GHD groups. Our data support the hypothesis that LCN2 plasmatic levels increase in metabolic syndrome. As previously shown (4), different inflammatory patterns characterize the two pathological conditions. However, the correlation between HOMA index and LCN2 suggest a possible modulatory action of LCN2 on insulin resistance in normal subjects and partial GHD ones.
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Diabetes Mellitus and Glucose Metabolism

IMPACTS OF METABOLISM ON CLINICAL CHALLENGES

Epinephrine Is Essential for Normal Renal Glucose Reabsorption via the Glucose Transporter GLUT2

Arwa Mahmoud Elsheikh, MBBS[1], Leticia M. de Souza Cordeiro, PhD[2], Nagavardhini Devisetty, PharmD[2], Steven N. Ebert, PhD[3], Kavaljit H. Chhabra, MPharm, PhD[2].
[1]University of Rochester Medical Center, Rochester, NY, USA, [2]University of Rochester, Rochester, NY, USA, [3]University of Central Florida, Orlando, FL, USA.

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Humans and mice with Melanocortin 4 receptor (MC4R) deficiency remain protected from hyperglycemia despite chronic obesity and insulin resistance. We have observed that elevated glycosuria in MC4R deficient mice protects them from hyperglycemia. Moreover, our results indicate that circulating epinephrine may couple MC4R signaling with kidney glucose reabsorption. However, the direct role of epinephrine in regulating kidney glucose reabsorption remains unclear. We hypothesize that epinephrine is essential for maintaining glucose homeostasis via kidney glucose reabsorption. To test this hypothesis, we performed oral glucose tolerance tests (OGTTs) and intraperitoneal insulin tolerance tests (ITTs) in phenylethanolamine-N-methyltransferase (*Pnmt*) knockout (KO) mice that specifically lack epinephrine but have normal norepinephrine levels. *Pnmt* KO mice exhibited reduced insulin sensitivity compared to their Wild-Type (WT) littermates (Area under the curve for ITT: 9,700±256 vs. 8,482±417 mg/dL.min, p<0.05). Paradoxically, we observed improved rather than impaired glucose tolerance in *Pnmt* KO mice compared to their WT controls (Area under the curve for OGTT: 32,546±1,592 vs. 40,058±1,918 mg/dL.min, p<0.05). To ascertain if *Pnmt* KO mice, like MC4R deficient mice, show elevated glycosuria, we quantified their 24 urine glucose levels after oral glucose (250 mg) challenge. Indeed, *Pnmt* KO mice demonstrated elevated glycosuria compared to their WT littermates (Urine glucose: Baseline, 24.63±2.2 vs. 11.14±0.82 mg/dl; post glucose challenge: 67.83±5 vs. 16.09±1.13 mg/dl, p<0.001), again validating the phenotype similar to that of MC4R deficient mice. To determine the glucose transporters involved in mediating elevated glycosuria in the *Pnmt* KO mice, we measured the levels of different renal glucose transporters using western blot. We found that GLUT2 was decreased by ~26% in *Pnmt* KO mice compared to their WT littermates. Levels of other glucose transporters were not changed, indicating that suppression of renal GLUT2 mediates elevated glycosuria in the epinephrine deficient mice. We validated the direct effect of epinephrine on GLUT2 levels in vitro using mouse primary renal proximal tubule epithelial cells. Indeed, epinephrine selectively increased GLUT2, but did not affect other glucose transporters in the mouse kidney primary cells. Our findings establish the essential role of epinephrine in glucose reabsorption via the renal glucose transporter GLUT2. Therefore, modulating the renal adrenergic system, or, kidney-specific GLUT2 may afford alternative strategies to regulate glycosuria and ultimately mitigate diabetes.

Reproductive Endocrinology

CLINICAL STUDIES IN FEMALE REPRODUCTION I

AMH Is Higher Across the Menstrual Cycle in Early Post-Menarchal Girls Than in Ovulatory Women

Madison T. Ortega, BS[1], Lauren Carlson, BS[2], John McGrath, MA[3], Tairmae Kangarloo, BS[4], Judith Mary Adams, RN[5], Patrick M. Sluss, PHD[6], Geralyn Mary Messerlian, PHD[7], Natalie Shaw, MD[1].
[1]NIEHS, Durham, NC, USA, [2]NIEHS, Raleigh, NC, USA, [3]SSS, Durham, NC, USA, [4]Massachusetts General Hospital, Boston, MA, USA, [5]MA Gen Hosp, Boston, MA, USA, [6]MA Gen Hosp, Olympia, WA, USA, [7]Women & Infants Hosp, Providence, RI, USA.

SAT-029

Ovaries of young girls contain healthy and degenerating follicles from the primordial to antral stage, suggesting coordination of growth and atresia. At age 6 yrs, antral follicle (AF) number and size increase; by late puberty, AF count is higher than at any other life stage. The discovery of AMH, a biomarker of AFs, has facilitated the study of the immature ovary. AMH, a granulosa cell product of preantral and small AFs, inhibits primordial follicle growth and AF selection. As a marker of AF count, AMH should be highest during puberty, yet cross-sectional studies suggest that AMH peaks in the mid-20's. In the current studies

we compared AMH levels in early post-menarchal girls and regularly cycling adults. The rich phenotypic data available for this adolescent cohort (Sun 2019) was used to investigate further the relationship between AMH, LH, FSH, and sex steroids, and the propensity for anovulatory cycles (ANOV) in girls. 23 healthy girls (12.8–17.6 yrs;1.7±0.2 yrs post-menarche; 56% overweight/obese [OB]) underwent hormone measurements and pelvic ultrasounds during 2 consecutive menstrual cycles. Cycles were classified as ovulatory (OV) based on an LH and E2 peak and P4 >1.65 ng/mL (Sun 2019). AMH was measured in a random subset of samples (5x/subject) with the Ansh ultrasensitive ELISA. Maximum average ovarian volume (VOL) was calculated in the absence of a dominant follicle. Hormones were compared with data from 32 historic adult controls (18–34 yrs; 44% OB) with regular cycles (Lambert-Messerlian 2016). In adults, AMH was measured during the follicular and luteal phase of an OV (5x/subject) using the Ansh assay. AMH was compared among groups using a mixed model. AMH (in adults), LH (in both) and androgens (in girls) were natural log-transformed (ln) before analysis. 11 girls had 2 OV, 5 girls had 1 OV, and 5 girls had no OV; 2 could not be classified due to loss to follow-up. Girls had higher AMH than women (5.2 ± 0.3 vs. 3.3 ± 0.4 ng/mL; $p<0.01$) and girls with more OV tended to have lower AMH than those with ANOV (2 OV 4.5 ± 0.2, 1 OV 5.7 ± 1.1, 0 OV 6.8 ± 1.1 ng/mL; p=0.1). In girls, AMH correlated with ln_LH (r=0.4, p=0.02), ln_a'dione (r=0.4, p=0.04), ln_testosterone (r=0.5, p=0.02) and VOL (r=0.6, p=0.01) but not with FSH, E2, or BMI. In women, AMH correlated with E2 (r=-0.4, p=0.03) and not with ln_LH or BMI. Within-person variability in AMH was similar in girls and adults (CV 18%). During the early post-menarchal years, AMH levels exceed those of adults with OV, particularly among girls with ANOV, and correlate with LH and androgens. The finding of higher AMH in adolescents is consistent with previous studies demonstrating a peak in AF count during this stage of development. Investigation into how the normal ovary matures and is pruned of excess AFs, either by increased recruitment and growth or by atresia, may provide insights into the pathogenesis of PCOS, wherein follicles are arrested at the pre-antral and antral stage.

Bone and Mineral Metabolism

NEW INSIGHTS INTO PTH AND CALCIUM RECEPTOR SIGNALING

A Novel Ex Vivo Live-Cell Interrogative Assay of Human Parathyroid Tissue Reveals Distinct Mechanisms of Calcium Sensing Failure in Primary, Secondary, and Tertiary Hyperparathyroidism

Jie Zhang, MD, PhD[1], Run Zhang, MS[2], Jessica Foft, BS[2], Catherine Starks, MS[2], Jessica Erin Gosnell, MD[2], Sanziana Roman, MD[2], Julie Ann Sosa, MD[2], James Koh, PhD[2].
[1]China-Japan Friendship Hospital, Beijing, China, [2]University of California, San Francisco, San Francisco, CA, USA.

OR07-04

Disruption of calcium homeostasis is common to all forms of hyperparathyroidism (HPT), but the underlying biochemical mechanisms that distinguish the various forms of HPT pathology remain poorly characterized. We previously have observed that the kinetics and amplitude of CASR-mediated signaling vary significantly among parathyroid (PT) adenomas and found specific functional and gene expression profiles preferentially associated with increased risk of bone density loss. While these data established a clear connection between CASR activity and clinical phenotype, a direct comparison of the kinetics of PTH secretory behavior between normal and neoplastic intact human PT tissue has yet to be performed. Utilizing eucalcemic normal human organ donor tissues (n=3) as a reference standard, we examined a series of cryopreserved live PT tissue specimens obtained from patients with primary (n=9), secondary (n=12) and tertiary (n=5) HPT. PT tissue fragments matched for viability, mass, and cellular content were placed on permeable membranes and exposed to a series of extracellular calcium concentrations over equivalent time intervals of challenge and normocalcemic recovery to interrogate dynamic PTH secretory induction or suppression. As expected, normal tissue exhibited a sigmoid response curve indicative of allosteric calcium-mediated inhibition, with a mean EC50 of 0.95 mM (95% CI: 0.859–1.254). In contrast, the majority of primary HPT adenomas (n=6) displayed a concave response curve indicative of non-competitive inhibition, consistent with a primary sensing deficit, such as loss of CASR expression. Two distinct PTH secretory behaviors were observed in secondary HPT specimens. One subset (secondary type 1, n=4) retained a sigmoid response curve but with a modest EC50 increase (mean EC50=1.50 mM, 95% CI: 1.41–1.61) and maximal suppression similar to normal tissue, features reflective of competitive inhibition in response to elevated calcium. This pattern could indicate enhanced CASR antagonist activity relative to normal tissue. A second subset, (secondary type 2, n=8) demonstrated a large EC50 shift (mean EC50=2.46 mM; 95% CI: 1.844–2.621), a sigmoid response curve, and an elevated threshold of persistent PTH secretion at high calcium conditions. These parameters are suggestive of non-competitive inhibitory behavior, consistent with loss of a CASR-dependent downstream effector. Three of the primary HPT adenomas shared this response phenotype. Of the tertiary specimens, four matched the primary HPT adenoma pattern, while one exhibited secondary type 2 behavior. These results reveal a series of progressively attenuated dynamic response patterns, where PTH secretion becomes increasingly uncoupled from extracellular calcium sensing. These findings suggest that primary, secondary, and tertiary HPT arise through distinct mechanisms of calcium sensing failure.

Diabetes Mellitus and Glucose Metabolism

TYPE 1 DIABETES MELLITUS

Rare Case of 48 XXYY Syndrome with Suspected Type 1 Diabetes Mellitus

Hassaan B. Aftab, MD, Faryal Sardar Mirza, MD, FACE.
University of Connecticut Health Center, Farmington, CT, USA.

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Background: 48 XXYY syndrome is a rare aneuploidy characterized by the presence of an extra X and Y chromosome in males. Patients share features of Klinefelter