of IGF-I levels in patients during Period 2, revealed that the overall mean within-patient percent change of IGF-I levels was 15.27 ± 12.20 (range: 0-41.5). The mean duration of follow up during this period, after patients were already treated for ≥12 weeks with injectable SRL, was 1.72 (± 1.29) months. The variability observed in Period 2 was similar to that observed in the entire sample evaluated in Period 1. No significant differences were found in the mean IGF-I percent change between any demographic or baseline characteristic subgroup examined. **Conclusion:** IGF-I levels fluctuate in patients with acromegaly who are responsive to injectable SRLs. These fluctuations are wide and can be up to 81% higher than the lowest (most controlled) value, with an average increase of approximately 20%. Significant IGF-I increases were observed at the end of the long acting SRL injection interval.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS II

Bisphosphonate and Denosumab Refractory Hypercalcemia of Malignancy: What Else Is at Play?

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MON-335

Hypercalcemia of Malignancy has been historically responsive to anti-resorptive agents. However, when multiple mechanisms contribute, it may be difficult to treat with one modality. This case highlights the importance of the work up in treatment of hypercalcemia in a low PTH state. A 44 yo M with h/o high grade metastatic spindle cell neoplasm with skeletal metastasis was admitted with hypercalcemia. He reported some constipation prior to presentation, however denied confusion. His vital signs were notable for HR of 86 bpm and BP of 112/75 mmHg. Labs at admission were remarkable for an uncorrected Ca of 16.1 (8.8-10.3 ng/mL), a phosphorus (Phos) level of 3.3 mg/dL (2.5-4.5 mg/dL), a PTH level of 11 pg/mL (15-65 pg/mL), PTHrP level of 134 pg/mL (14-27 pg/mL), a 25 OH vit D level of 11 ng/mL (30-100 ng/mL), and a BUN/Cr and GFR of 34/2.38 (8-22 mg/dL/0.5-1.3 mg/dL) and 32 ml/min/m2. He was given intranasal calcitonin and ergocalciferol, then received 2mg IV of zolendronic acid, which reduced the patient's Ca level to a nadir of 6.6 ng/mL in 5 days. On the next admission serum Ca was elevated to 15.7 ng/dL, which did not respond to zolendronic acid. Given that patient's Ca was refractory to zolendronic acid, denosumab was given but had no response. He then underwent surgery for cord compression and was given dexamethasone (dex) 4mg IV Q6h post-op. His Ca responded quickly to dex, with a nadir to 9.2 ng/dL, however his Ca became elevated after cessation. Given response to dex, vit D 1,25 OH level was sent and was elevated at 94 pg/mL (18-72 pg/mL). In addition, given his inappropriately normal Phos level in the setting of low PTH, FGF23 was sent and came back elevated at 473 RU/mL (<180 RU/mL). This was likely due to increased bone turnover and release of FGF23. He was discharged with a Ca level of 12.5 ng/mL, however was found to have an elevated Ca to 14.9 ng/mL on presentation to clinic. Given concern that Vit D 1,25 OH, PTHrP and direct bony involvement were all contributing to his hypercalcemia, patient was started on IVF and dex IV. His calcium responded 11.5 ng/mL and was then transitioned to PO dexamethasone and plaquenil. The most likely explanation for this phenomenon is malignancy induced cytokine/PAMP release, which stimulates 1-alpha hydroxylase in tumor macrophages to convert 25 OH D to 1,25 OH D. This was supported by his elevated 1,25 OH D level and a decreased 25 OH D, which suggests that 25 OH D was used as substrate by activated macrophages. This case highlights the importance of ancillary work up of hypercalcemia when a patient's calcium is refractory to standard anti-resorptive therapy. Moreover, it shows the need for a systematic approach when treating hypercalcemia.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

Musashi Exerts Translational Control Within Anterior Pituitary Cells of the POU1F1 Lineage.

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SAT-284

The activation of transcription factor *Pou1f1* at embryonic day 13 gives rise to the pituitary populations of somatotropes, lactotropes, and thyrotropes and these populations maintain expression of *Pou1f1* throughout life. The Musashi family of RNA regulatory proteins is known to regulate stem cell fate by repressing translation of target mRNAs needed for differentiation. Previously our lab has shown that female *Lepr*-null somatotropes have reduced POU1F1 protein levels but do not have changes in *Pou1f1* mRNA expression. Stimulation with leptin increased the POU1F1 protein levels 3-fold, but did not change *Pou1f1* mRNA suggesting a post-transcriptional mechanism for leptin's regulation of *Pou1f1*. An *in silico* analysis indicated the presence a number of potential regulatory elements (MBEs) within the *Pou1f1* mRNA 3' UTR, including 8 consensus Musashi binding elements. Interestingly, we found *musashi* mRNA and protein levels were increased in *Lepr*-null somatotropes. This suggested that leptin regulates the expression of *musashi* in somatotrope populations and may be a candidate translational regulator of the *Pou1f1* mRNA. We verified that MSI binds directly to the *Pou1f1* mRNA 3' UTR MBEs by EMSA *in vitro* and exerts translational repression (using reporter mRNA assays in transfected cell populations). Single cell RNA sequencing of pituitary cells from control male and female mice indicates that *MSI* and *Pou1f1* mRNAs are co-expressed in somatotropes, lactotropes as well as thyrotropes. Immunocytochemical analyses confirmed that Musashi protein is present in mixed and purified somatotrope populations. Furthermore, immunoprecipitation with Musashi1 antibody showed a 5-fold enrichment of *Pou1f1* mRNA in control female

mouse pituitaries. These findings point to a critical *in vivo* role for Musashi-mediated mRNA translational regulation within the Pou1f1 lineage and specifically in the control of somatotrope maturation and response to metabolic cues.

Diabetes Mellitus and Glucose Metabolism

CLINICAL AND TRANSLATIONAL STUDIES IN DIABETES

Glucokinase Within the Hypothalamic Paraventricular Nucleus Is Important in GLP-1 Release

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MON-666

When glucose is taken orally more insulin is secreted than when glucose is injected directly into the bloodstream. This is known as the incretin effect. Glucagon like peptide 1 (GLP-1) is one of the hormones responsible for this effect. GLP-1 is released from enteroendocrine L-cells in the gut in response to oral glucose intake. GLP-1 increases insulin synthesis and secretion. Release of GLP-1 is thought to be solely dependent upon gastrointestinal tract mechanisms. Here we identify a brain mechanism via the hypothalamic paraventricular nucleus (PVN) which is important in the release of GLP-1 in response to oral glucose. The role of the paraventricular nucleus in glucose homeostasis was previously unknown. We found that a glucokinase dependent glucose sensing mechanism in the PVN works in conjunction with the gut to regulate GLP-1 release. We show that increasing expression of GK (sense GK, sGK) into the PVN improves glucose tolerance (15 minutes glucose: GFP: 8.93±0.27mmol/L, n=11; sGK: 7.72±0.22mmol/L, n=12; $p<0.01$ and 15 minutes insulin GFP: 2.84±0.14mmol/L, n=11; sGK: 3.73±0.27mmol/L, n=12; $p<0.01$) and increases GLP-1 release in response to oral glucose (GFP: 6.16±0.18mmol/L, n=11; sGK: 6.90±0.26mmol/L, n=12; $p<0.01$). On the contrary decreasing expression of GK (antisense GK, asGK) in the PVN worsens glucose tolerance (30 minutes glucose: GFP: 8.22±0.28mmol/L; asGK: 9.46±0.24mmol/L, n=8; $p<0.01$ and 15 minutes insulin: GFP: 4.07±0.37mmol/L; asGK: 2.25±0.17mmol/L, n=8; $p<0.001$) and blunts (GLP-1 release 30 minutes GLP-1: GFP: 6.93±0.25pMol/L, n=8; $p<0.01$ asGK: 5.47±0.13pMol/L, n=8; $p<0.001$). Our results demonstrate that glucosensitive GK neurones in the PVN, are important to the response to oral glucose and the subsequent release of GLP-1.

Reproductive Endocrinology

BASIC MECHANISMS IN REPRODUCTION: FROM BEGINNING TO END

Placentas from Obese Women Are Resistant to the Effect of Insulin on Triglyceride Content Ex Vivo

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Background: Obesity affects 25% of pregnant women and is associated with a higher risk of neonatal complications, such as macrosomia and increased adiposity. The placenta may contribute to neonatal adiposity by accumulating and transferring excess lipid in response to maternal hyperinsulinemia. We previously found that insulin promotes a 3-fold increase in placental triglyceride (TG) content in lean women. We hypothesized that obese women have higher placental insulin resistance compared to lean women[FC1] with respect to TG content. **Methods**: Healthy, lean women (n=12; mean age 34±1 yrs; BMI 22±0.4 kg/m^2) and non-diabetic, obese women (n=9; mean age 32±2 yrs; BMI 33±0.4 kg/m^2, $p<0.0001$) consented for placenta collection at elective c-section under fasting conditions. Placental villous explants were immediately flash frozen or cultured for 24 hours, starved, then treated for 48 hours with 0.1nM, 1nM, 10nM, or 100nM of insulin, or vehicle. Lipids were extracted from basal and treated explants using a chloroform-methanol separation protocol. TG content was quantified by spectrophotometer and normalized to weight. Data were analyzed by two-way ANOVA. **Results**: Basal placenta tissue from obese women contained a 1.5-fold higher level of TG compared to lean women (9.4±0.5 vs 5.7±0.5 mcg/mg, $p=0.001$). Placental response to insulin in lean women peaked at 1nM insulin (20.2±3.3 mcg/mg), and plateaued at higher doses of 10nM (18.6±3.3 mcg/mg) and 100nM (22.8±2.8 mcg/mg, p=NS respectively). In contrast, placenta explants from obese women required the highest insulin dose of 100 nM for maximal response (23.6±3.2 mcg/mg), and showed a gradual dose response from 0.1 nM insulin (9.5±2), 1nM (14.8±2), 10 nM (16.9±3). At 100nM insulin, the difference in TG content was variable, but on average was 2-fold higher than vehicle treated placenta (vs 11.8±2.5[FC2] [AA3] mcg/mg, $p=0.002$). **Conclusion**: Our findings indicate that placenta from obese women develop insulin resistance similar to peripheral tissues, which can be overcome by high insulin doses. This placental insulin resistance likely occurs in response to chronic hyperinsulinemia, leading to interference of insulin signaling pathways, and may protect the neonate from excessive nutrient flux.

Thyroid

THYROID DISORDERS CASE REPORTS I

Viral-Induced Autoimmune Hyperthyroidism in an Adult Patient Without Established Thyroid Disease

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SUN-500

Viral-Induced Autoimmune Hyperthyroidism in an Adult Patient Without Established Thyroid Disease