heteromerize with FSHR, as well as in KO HEK293 cells unable to produce a molecular complex associated with GPER inhibiting cAMP. GPER/FSHR coexpression is confirmed in secondary follicles from paraffin-embedded tissues of human ovary by immunohistochemistry, suggesting that FSHR-GPER heterodimers could be physiologically relevant *in vivo* for inhibiting cAMP-linked apoptosis. Most importantly, FSHR and GPER co-expression correlates in hGLC from FSH-normo-responder women undergoing assisted reproduction, while it is not in hGLC from FSH-poor-responders, where increasing *FSHR* mRNA levels do not correspond to increasing *GPER* mRNA levels. We demonstrate that death signals in atretic follicles are delivered through overexpressed FSHR and inhibited by FSHR/GPER heteromerization, activating anti-apoptotic pathways. This finding unveils a novel working model of the physiology of dominant follicle selection and the relationship between FSH and estrogens.

Bone and Mineral Metabolism

CLINICAL ASPECTS OF OSTEOPOROSIS AND VITAMIN D ACTION

Vitamin D Metabolism in Patients with Acromegaly: A Case-Control Pilot Study

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Objective: to study the differences in the metabolism of vitamin D and calcium-phosphorus metabolism in patients with an active phase of acromegaly in comparison with healthy individuals. Materials and methods: The study included 8 patients with an active acromegaly, median age 36.5 ± 6.25 years, BMI 27.9 ± 1.95 kg/m2, IGF-1 907.3 ± 239 ng/ml, as well as 8 conditionally healthy individuals selected by age, sex and level of 25(OH)D determined by the immunochemiluminescent method (DEQAS certified). All participants were tested for calcium-phosphorus metabolism, PTH, and vitamin D metabolites by HPLC/MS-MS (25(OH)D3, 25(OH)D2, 3-epi-25(OH)D3 and 24,25(OH)2D3) before oral administration of 150 000 IU of an aqueous solution of cholecalciferol and 7 days after administration. Results: In the Acromegaly group, on the 7th day after taking the drug, there was a statistically significant increase in 25(OH)D3 (89.8 ± 10.5 vs. 54.1 ± 14.8 nmol/L), 3-epi-25(OH)D3 (9.0 ± 2.6 vs. 3.3± 1.1 nmol/L) and 24,25(OH)2D3 (8.3 ± 1.9 vs. 6.4 ± 2.1 nmol/L), and a decrease of 25(OH)D2 (0.8 ± 0.2 vs. 1.1 ± 0.3 nmol/L) and a ratio of 24,25(OH)2D3 to 25(OH)D3 (0.1 ± 0.02 vs. 0.13 ± 0.03). A statistically significant increase in albumin-adjusted calcium was also noted (2.39 ± 0.14 vs. 2.31 ± 0.13 mmol/L). The medians of the levels of PTH and phosphorus initially were 27.1 ± 13.5 pg/ml and 1.6 ± 0.3 mmol/l and did not change by day 7 after taking the drug; creatinine and magnesium levels also remained the same. The level of calcium-creatinine ratio in a single portion of urine (CCR) was initially within the reference interval for all patients, its median did not change by day 7, however, in two patients there was a clinically insignificant increase higher than the upper limit of the reference interval; the phosphorus-creatinine ratio in a single portion of urine increased significantly. In the control group, after taking cholecalciferol similar changes in the levels of the studied vitamin D metabolites were observed, the levels of PTH also remained the same, however, there were no changes in the median biochemical parameters of blood and urine by day 7 after drug intake. Among the studied vitamin D metabolites, there were initially no significant differences between the groups; on day 7 a difference was recorded for the level of 3-epi-25(OH)D3 (9.0 ± 2.6 in the Acromegaly group vs. 18.8 ± 8.9 nmol/L in the control group). Among the biochemical parameters in the Acromegaly group higher levels of ionized blood calcium (1.14 ± 0.05 vs 1.1 ± 0.03 mmol/L), blood phosphorus (1.61 ± 0.26 vs 1.15 ± 0.09 mmol/L) and CCR were observed. Conclusion: Loading dose of cholecalciferol in patients with acromegaly is associated with less production of 3-epi-25(OH)D3, and results in lower inactive fraction of vitamin D than in healthy controls. More studies are needed to evaluate the effect of 1.25(OH)2D3 level on calcium-phosphorus metabolism in acromegaly.

Genetics and Development (including Gene Regulation)

G PROTEIN-COUPLED RECEPTOR SIGNALING IN ENDOCRINE SYSTEMS: NOVEL MECHANISMS IN HEALTH AND DISEASE

USP8 Genetic Variants May Contribute to the Development of Bilateral Adrenal Hyperplasia and ACTH-Independent Cushing Syndrome

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Background: Bilateral adrenocortical hyperplasias (BAHs), including primary pigmented nodular adrenocortical disease (PPNAD), isolated micronodular adrenocortical disease (iMAD) and primary macronodular adrenocortical hyperplasia (PMAH), are rare causes of ACTH-independent Cushing syndrome (CS). PPNAD and iMAD usually present in children or adolescents as multiple small (<1cm), cortisol-producing adrenocortical nodules. On the other hand, PMAH is most frequently identified in older patients with multiple large adrenal nodules. Most patients with PPNAD have *PRKAR1A* mutations whereas patients with PMAH may harbor variants in other genes (*ARMC5, MC2R, GNAS, APC, MEN1).* Even though several genes have been associated with ACTH-independent CS, there are still cases that the genetic cause has not been elucidated.

Clinical cases: Herein, we present two unrelated patients with ACTH-independent CS that harbor *USP8* gene variants. *USP8* is mainly known for being mutated in Cushing disease but as a deubiquitinase it may be involved into the Wnt/β-Catenin signaling pathway.

The first patient was diagnosed with BAH on prenatal ultrasound (26 gestational week) and subsequently required

bilateral adrenalectomy for CS as she had virilization, hirsutism, hypertension and cardiac hypertrophy 9 weeks old. Adrenalectomy revealed that she had iMAD. She also presented with hemihypertrophy of the right leg, labia and mild newborn hypoglycemia, however she was negative for Beckwith-Wiedemann mutation. Gene analysis of *PRKAR1A* did not reveal any mutations. After whole exome sequencing (WES), we found a novel heterozygous *USP8* variant (c.1387_1393delinsT, p.Ala463_Ile465delinsPhe) at germline level and loss of heterozygosity (LOH) at tumor level. Immunohistochemistry showed significantly lower expression of USP8 protein in both of her adrenals compared to a control tissue.

The second case is a 59-year old female with osteoporosis who failed to suppress cortisol levels after low dose dexamethasone administration. MRI revealed an adenoma on the right adrenal (2.6cm). She underwent right adrenalectomy and was found to have PMAH. We performed WES in germline level and we detected a novel heterozygous missense *USP8* variant (c.287A>G, p.Lys96Arg) that is present also at tumor level. Immunohistochemistry showed significantly lower expression of USP8 protein in her adrenal tumor compared to the control tissue. No LOH was identified.

Conclusion: This is the first report of the association of *USP8* in ACTH-independent CS and the preliminary findings support UPS8 involvement in the development of adrenocortical disease. We are currently performing further in vitro studies to evaluate the effect of these two *USP8* variants into the canonical Wnt pathway which is commonly involved in adrenocortical disorders.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY II

CXCR2 Repression by Glucocorticoids in Adipose Tissue

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Obesity-induced type 2 diabetes (T2D) is a significant risk factor of cardiovascular disease (CVD), which affects 28.1 million adults in the United States. Adipose tissue chronic inflammation is one of the main factors that drive obesity-induced insulin resistance (IR) and T2D. Despite several studies that have shown a link between obesity, adipose tissue inflammation, and IR/T2D, the mechanisms underlying this association are not well understood. Synthetic glucocorticoids are widely used for their potent anti-inflammatory actions; however, their use is hampered due to off-target side effects. Glucocorticoids exert profound effects on adipose tissue, including the regulation of adipocyte metabolism and immune functions. However, whether their effects on adipose tissue are positive or negative it is still a controversial topic. Genome-wide microarray data obtained from adipocyte-specific glucocorticoid receptor (GR) knockout (AdipoGRKO) mice showed that lack of GR leads to a significant increase in the expression of pro-inflammatory genes in white adipose tissue (WAT). Moreover, WAT isolated from adipoGRKO mice demonstrated significant increase in immune cell infiltration, which correlates with our gene expression data. Among the most up-regulated genes, we found the C-X-C Motif Chemokine Receptor 2 (CXCR2), which is a critical mediator of chemotaxis to the sites of inflammation. Although studies have shown the presence of CXCR2 in adipocytes and suggested the contribution of CXCR2 signaling in adipocyte development, its role in obesity-driven adipose tissue inflammation is unknown. This led us to hypothesize that adipocyte specific administration of glucocorticoids can reduce obesity-induced adipocyte inflammation by inhibiting CXCR2 gene transcription and signaling. Our in vitro studies using 3T3-L1 cells derived adipocytes showed that treatment with the synthetic glucocorticoid, Dexamethasone (Dex) led to a significant repression of CXCR2 mRNA and protein levels. Correlating with these results, Dex treatment significantly inhibited macrophage migration to adipocytes in a mechanism dependent on GR activation and repression of CXCR2. Furthermore, these results were recapitulated in vivo. Together our findings suggest that local delivery of glucocorticoids to adipose tissue could ameliorate inflammation and reduce the risk of developing IR and T2D.

Neuroendocrinology and Pituitary

PITUITARY TUMORS: TRIALS AND STUDIES

Is the Improved Glucose Homeostasis in Patients with Acromegaly Treated with Pegvisomant Caused by Improved Glucagon Secretion?

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Context: Active acromegaly is associated with impaired glucose metabolism, which improves upon treatment. Treatment with first generation somatostatin analogues (SSA) has a detrimental effect on insulin secretion, but the effect on glucose homeostasis is neutralized by the reduction in growth hormone (GH) and Insulin-like growth factor-1 (IGF-1). Treatment with GH receptor antagonists has a more favorable effect on glucose homeostasis.

Objective: To describe the secretion of glucose, insulin, glucagon, glucagon-like peptide-1 (GLP1), and glucose-dependent insulinotropic polypeptide (GIP) in surgically treated patients with acromegaly treated or not with somatostatin analogues, either as monotherapy (SSA) or in co-treatment with pegvisomant (SSA+PEG), respectively, compared to healthy controls.

Methods: Descriptive study of data from 23 surgically treated, non-diabetic patients with acromegaly and 6 healthy controls. After an overnight fast, all participants