OR04-06

Adaptive thermogenesis is important for the control of body temperature (Tb) and maintenance of body weight, and it is primarily regulated by sympathetically-driven brown adipose tissue (BAT). Studies indicate that muscle is also involved in thermogenic regulation. $G_s\alpha$ couples to ligands and receptors, including β-adrenergic receptors, to increase intracellular cAMP. Our previous studies have showed that mice with adipose-specific $G_s\alpha$ deficiency had inactive BAT and impaired cold tolerance. To determine whether $G_s\alpha$/cAMP signaling in skeletal muscle compensates for loss of BAT thermogenesis, we generated mice with $G_s\alpha$ deficiency in adipocyte tissue alone (AdipGsKO), in skeletal muscle alone (SkMGsKO) or in both (AdipSkMGsKO). Compared to control mice, AdipGsKO and SkMGsKO mice had normal body weight, while AdipSkMGsKO showed reduced body weight with normal food intake and energy expenditure. Both AdipGsKO and AdipSkMGsKO mice had elevated fasting glucose levels, but similar glucose tolerance to control or SkMGsKO mice. SkMGsKO mice displayed reduced insulin sensitivity. When acutely exposed to 6°C for 3 hours, AdipGsKO and AdipSkMGsKO mice rapidly decreased their Tb, indicating that they are sensitive to acute cold exposure, consistent with their inactive BAT. To assess adaptation to chronic cold, mice were exposed to gradually declining ambient temperature from 22°C to 6°C with a daily decrease of 2°C and were then kept at 6°C for 5 days. As expected, both AdipGsKO and AdipSkMGsKO mice failed to stimulate BAT UCP1 by cold adaptation. Unexpectedly, AdipGsKO mice maintained normal Tb similar to control and SkMGsKO mice. However, AdipSkMGsKO mice started to rapidly drop their Tb when ambient temperature declined to 14°C and 85% of SkMGsKO mice (11/13) died before the end of experiment. These results suggest that when there is a lack of BAT function, $G_s\alpha$/cAMP signaling in muscle plays an essential role for mice to survive in response to chronic cold challenge.

Neuroendocrinology and Pituitary

PITUITARY AND NEUROENDOCRINE CLINICAL TRIALS AND STUDIES

Serum Cell-Free Methylation-Based Signatures Distinguishes Pituitary Tumors According to Functional Status and from Other Neoplasia: A Liquid Biopsy Approach.

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OR32-03

Background: Several reports have indicated that distinct epigenomic patterns of pituitary tumors (PT), specifically DNA methylation, distinguish these tumor tissues according to their functionality and could be involved in their pathogenesis. Thus far, molecular diagnosis and classification criteria that guide clinical management of these tumors rely on the tissue profiling obtained by invasive surgical approaches (e.g. excision). However, increasing evidence confirmed that central nervous system (CNS) tumors release cell material into the circulation creating an opportunity for molecular profiling of these tumors using a blood-based liquid biopsy. Considering that 1) the pituitary portal system and the invasion of the cavernous system by PT may facilitate the spillage of tumor cell material into the bloodstream and 2) the stability, cell-specificity and reportedly the role of DNA methylation in PT, we hypothesized that liquid biopsy would be feasible to detect and define specific methylation-based signatures in the serum of patients harboring PT. **Methods and Findings:** We conducted analyses of the methylomes of paired serum circulating cell-free DNA (cfDNA) and tumor tissue from patients harboring PT (EPIC array) to identify serum-derived pituitary tumor-specific methylation-based signatures (sPTMet n=37) in a cohort comprised by 13 patients with pituitary macroadenomas (9 males; median age: 62; 9 Nonfunctioning/4functioning, 6 invasive/7noninvasive), 4 controls (non-tumor) and patients with other CNS tumors or conditions (114 gliomas, 6 meningiomas, 1 brain metastasis, 1 colloid cyst, 6 radiation necrosis). Unsupervised and supervised analysis indicated that the serum methylome from patients harboring PT was distinct from controls and other CNS diseases. Using the sPTMet as input into a machine learning algorithm, we generated a PT score that classified the serum of an independent cohort as PT or non-PT, with high accuracy. We identified serum-derived differentially methylated probes (DMP, n=3288) that distinguished PT according to their function (functioning and nonfunctioning). When overlapped with an independent cohort, these DMP also distinguished PT tissue according to their functional status. **Conclusion:** Our results showed the feasibility to identify PT-specific methylation signatures by profiling the methylome of serum cfDNA from patients with PT. These signatures distinguished PT from other CNS tumors and according to their subtypes. These results underpin the potential role of methylation profile and liquid biopsy as a noninvasive approach to assess clinically relevant molecular features. Potentially, tumor-specific serum-derived methylation signature may be used as a diagnostic, prognostic and surveillance tool as well to identify actionable molecular markers in patients with PT.

Thyroid

BENIGN THYROID DISEASE AND HEALTH DISPARITIES IN THYROID II

Reverse T_3 in Patients with Hypothyroidism, Helpful or a Waste of Time?

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SUN-410

Background: The normal thyroid secretes T_4 (an inactive precursor), T_3 (the active hormone) and reverse T_3,

a biologically inactive form of T_3 that may block T_3 from binding to the thyroid hormone receptor. As about 15% of patients on L-T_4 replacement with a normalized TSH report continued fatigue and other hypothyroid symptoms, efforts are needed to understand this phenomenon. Decades ago, endocrinologists realized that in severe illnesses, rT_3 is often high and T_3 is often low and termed this "sick euthyroid syndrome". However, more recently, alternative or functional doctors have argued that high rT_3 is detrimental and can block T_3 from binding to the thyroid hormone receptor. Without peer-reviewed publications, these functional doctors rely heavily on rT_3 levels to treat patients that may have no other laboratory findings of hypothyroidism and often prescribe them L-T_3-only preparations to try to lower the rT_3.
Hypothesis: Patients on L-T_4 alone will more likely have an elevated rT_3 compared to patients on desiccated thyroid or L-T_4/L-T_3 therapy.
Methods rT_3 was measured in 98 consecutive patients seen in a tertiary Endocrinology clinic with possible or confirmed hypothyroidism (all with severe fatigue) with many of them were already treated with different thyroid preparations.
Results: The figure shows the 25%-75% quartiles, ranges and ratio of rT_3 above the normal range/patients in that category. The cutoff of 24 ng/dL (upper limit of normal for rT_3 at either Quest or LabCorp) is indicated by the line. Overall, 18 of the 98 patients had a rT_3 above the normal range. Patients on L-T_4 alone or desiccated thyroid plus L-T_4 had the highest levels of rT_3 and the highest % above the cut-off. Three of the patients with a high rT_3 were not on any thyroid medicine, and in 2 of them, the rT_3 normalized when repeated. The 8 patients with a high rT_3 on L-T_4 was a relatively high percentage (29%).
Conclusion: Measuring rT_3 may be helpful in patients who are already on T_4-containing thyroid treatments who still have hypothyroid symptoms. Based on this data, measuring rT_3 in most patients who are not taking thyroid medicine is not recommended, as only a very small percentage of them had an elevated rT_3. Future studies are needed to determine if high rT_3 levels correlate with hypothyroid symptoms and if adding L-T_3 or desiccated thyroid to hypothyroid patients on L-T_4 normalizes rT_3 and improves hypothyroid symptoms.

Neuroendocrinology and Pituitary

CASE REPORTS IN UNUSUAL PATHOLOGIES IN THE PITUITARY

Too Big to Be True, Too Young to Stroke!

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SUN-285

Background: Lactotroph adenomas are the most common type of pituitary adenomas and can cause infertility and menstrual irregularities in women; hypogonadism and gynecomastia in men.[1] Giant prolactinomas are an unusual subset of pituitary macroadenomas with limited literature available on their management.[2] We describe an unusual case of giant prolactinoma in a young man who presented with symptoms of stroke, that reversed with treatment with cabergoline. **Clinical Case:** 25-year old man presented with gradually progressing upper extremity weakness for evaluation of stroke. He reported stumbling into things when walking. There was a question of left sided facial droop and Bell's palsy in recent past. He reported recent weight gain and erectile dysfunction. He was noted to have left homonymous hemianopsia on exam in addition to left upper and lower extremity weakness. MRI Brain showed an enormous mass that filled the sella turcica, invaded the sphenoid sinus and right side of the skull base, invaginating deep into the base of the right cerebral hemisphere with mass effect on the pons, right-sided midbrain, right temporal lobe and right basal nuclei, measuring 6.3 X 5.5 x 7.5 cm. Pituitary hormonal evaluation showed elevated prolactin (PRL) level with dilution at 13,580 ng/mL, with low testosterone (T) level (total T 42 ng/dL, free T 10 pg/mL, SHBG 15 nmol/L). Thyroid and adrenal axes were intact with normal IGF-1 level. In view of very high PRL level, he was started on cabergoline 0.5 mg daily initially and decreased to every other day after 2 weeks as PRL level began to decline. In 8 months, PRL levels decreased to 1293.07 ng/dl (90% reduction) and prolactinoma decreased to 6.0 x 3.7 x 4.7 cm (56% volume reduction). Total and free T improved to 134 ng/dL and 31 pg/dL respectively. He experienced marked improvement in left hemianopsia, with resolution of weakness and slurred speech. Energy level and erectile dysfunction improved. Currently he is being maintained on 0.5 mg cabergoline every other day **Conclusion:** Giant prolactinomas are uncommon and can present with compressive symptoms, that can be mistaken as stroke. Treatment with anticoagulation may cause hemorrhage and apoplexy with worsening of symptoms.[1,2] There is limited data available regarding first line therapy for giant prolactinomas with 2 case reports where giant prolactinomas have been treated effectively with cabergoline.[3,4] It is important to recognize the cause of such symptoms, and treated where possible with effective medical therapy to prevent morbidity. **References:** 1. Moraes A et al., Giant prolactinomas: the therapeutic approach. Clin Endo (Oxf). 2013 Oct;79(4):447-56 2. Acharya SV et al., Giant prolactinoma and effectiveness of medical management. Endocr Pract. 2010 Feb;16(1):42-6 3. Ahmed, M, et al., Large Prolactinoma. NEJM 2010; 363:177 4. Masoud, R et al., Giant prolactinoma: case report. J Diabetes Metab Disord. 2013; 12: 3

Reproductive Endocrinology

REPRODUCTIVE ENDOCRINOLOGY: REPRODUCTIVE FUNCTION AND DYSFUNCTION ON DEVELOPMENT

Diagnostic Performance of Ovarian Morphology for Anovulatory Conditions in Lean and Overweight Women

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