Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

Thyroid Hormone Receptor Alpha Sumoylation Is Important for the Development of Adipose Tissue

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Abstract: Thyroid hormone (TH) plays an essential role in normal development. TH action requires binding to its receptor. There are two types of thyroid hormone receptor, alpha (THRA) and beta (THRB). THRB is important for regulation of the Hypothalamic-Pituitary-Thyroid axis and regulating cholesterol metabolism. THRA is involved in the development and the function of brain, adipose tissue, small intestine, bone and heart. Both THRA and THRB are post-translationally modified by small ubiquitin-like modifier (SUMO). Previously, we showed in an *in vitro* model that mutation of a THRA sumoylation motif impairs proliferation and differentiation of human primary white adipocytes. This is due to interference of the desumolyated THRA in the cell cycle at G1/S phase and disruption of PPAR signaling. To determine the *in vivo* effects of a desumoylated THRA, we generated a mouse model carrying a mutation of the *THRA* gene, which eliminates SUMO conjugation at lysine (K) 283. At 12 weeks of age, there was no difference in body composition (body weight, fat mass, and lean mass) in THRA mutant mice compared to wild-type (WT). From 12 weeks onward mutant mice and WT did not have significant change body weight compared to Wt mice. However, THRA sumoylation mutant mice had much lower percent body fat. Dissected WAT fat pads from mutant mice were significantly smaller compared to WT mice. Histological analysis showed that the cell size of white adipose tissue in mutant mice was significantly smaller than that in Wt mice as well. Serum leptin levels in the mutant mice were significantly lower than that in mice, consistent with reduced fat mass. We isolated fat stem cells from stromal vesicular fraction of 6 week old mice and found that the number of fat stem cells was significant less in mutant mice compared to those in WT mice. This data suggest that de-sumoylated THRA is associated with reduced fat stem cells at a young age, resulting in reduced adipose tissue mass in adult. THRA sumoylation is important for thyroid hormone modulation of fat mass.

Reference: (1) Yan-Yun Liu et al, JBC 2012 (2) Yan-Yun Liu et al., JBC 2015

Reproductive Endocrinology

MALE REPRODUCTIVE HEALTH THROUGHOUT THE LIFESPAN

Sexual Symptoms Predict All-Cause Mortality Independently of Sex Steroids in Ageing Men

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Background: The association between low testosterone (T) and higher mortality in men remains controversial. Most studies focus only on the association between total T (TT) and mortality. While TT declines with age, free T (FT) shows a greater fall, due to the rise in SHBG. Moreover, higher LH as well as sexual dysfunction, often co-existing with low T, have also been associated with mortality in ageing men.

Objective: To study the interrelationships between sex steroids, gonadotrophins and sexual symptoms with all-cause mortality in a large prospective cohort of European men.

Methods: 1913 community-dwelling men, aged 40-79, participated in the European Male Ageing Study (EMAS) between 2003-2005. Sexual symptoms were assessed via a validated questionnaire (EMAS-SFQ). Sex steroids were measured by mass spectrometry. In 5 of 8 EMAS centres, survival status was available until 1 April 2018. Cox proportional hazard models were used to study the association between hormones, sexual symptoms and mortality. Because of the wide age range at study entry, age was used as time-scale, instead of years since inclusion adjusting for age. Results were expressed as hazard ratios (HR) with 95% confidence intervals, adjusted for centre, BMI and smoking.

Results: 483 (25.3%) men died during a mean follow-up of 12.4±3.3 years. Men who died had a higher BMI (p=0.002), but smoking status did not differ. TT levels were similar in both groups, but FT was lower in those who died (mean±SD: 312±86 pmol/L vs 270±84, p<0.001) and LH was higher (5.7±3.3 U/L vs 7.8±5.8, p<0.001). Men in the lowest FT quartile had higher mortality risk compared to men in the highest quartile (HR 1.43 (1.06-1.95); p=0.021). Also men in the highest FSH quartile had increased mortality risk (HR 1.38 (1.02-1.88); p=0.036). However, there was no association with TT, E2 or LH. Men with 3 sexual symptoms had a higher mortality risk compared to men with no sexual symptoms (HR 1.77 (1.28-2.41); p<0.001). In particular erectile dysfunction and poor morning erections, but not lower libido, were associated with increased mortality (HR 1.40 (1.15-1.73); p=0.001; HR 1.30 (1.06-1.60); p=0.012; HR 1.14 (0.93-1.40); p=0.203 respectively). Further adjusting for TT and FT did not influence the observed HRs. Also in men with normal TT (>12 nmol/L), the presence of sexual symptoms increased mortality risk (HR 1.51 (1.15-1.97); p=0.003). Finally, men with TT<8 nmol/L and sexual symptoms had a higher mortality risk compared to men with normal TT and no sexual symptoms (HR 1.92 (1.05-3.52); p=0.035).

Conclusions: Men with the lowest FT and highest FSH levels have an increased mortality risk. Sexual symptoms, in particular erectile dysfunction, predict all-cause mortality independently of T levels. As both vascular disease and low T can influence erectile function, sexual symptoms can be an early sign for increased cardiovascular risk and mortality, as well as a sequela of low T.

Neuroendocrinology and Pituitary

PITUITARY TUMORS II

Giant Growth Hormone Secreting Pituitary Adenomas: A Single Institution Case Series

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The prevalence of growth hormone (GH)-secreting pituitary adenoma is around 11-13% of all pituitary adenomas. Giant GH-secreting pituitary adenomas (≥ 4 cm) are rare tumors, and its prevalence of among acromegalic patients is <5%.

This is a retrospective cohort study including patients with giant GH-secreting pituitary adenomas. The study population consisted of 10 patients (5 M/5 F). The mean age at diagnosis was 33.0±12.9 yrs (11-55 yrs). The mean delay between first symptom onset and diagnosis was 2.9 years. The most frequent symptoms were acral enlargement and facial changes (80%), followed by headache (70%) and visual deterioration (50%). One patient had epilepsy. Amenorrhea was presented in three females but obvious galactorrhea in two. The mean adenoma diameter was 42.6±4.7 mm (40-51 mm) at diagnosis. The vast majority of adenomas presented suprasellar extension (100%) or cavernous sinus invasion (80%). Cystic adenomas accounted for 50%. At presentation, mean GH and IGF-1 levels were 40.0±21.4 ng/mL (14.8-51.0) and 2.62±1.09 x ULN (1.08-3.96), respectively. Six patients presented with PRL cosecretion. At diagnosis maximal tumor diameter was not correlated with GH or IGF-1 levels.

All patients underwent pituitary surgery as first-line treatment. Three cases were treated with an endoscopic approach and four cases with a microscopic approach. Transcranial approach was also employed in three cases. Postoperative mean GH and IGF-1 levels were 14.9±16.1 ng/mL (0.6-51.0) and 2.25.±0.82 x ULN (1.48-3.74), respectively. After first surgery, only one patient had more than 50% reduction in IGF-1 levels. Five patients (50%) underwent repeat surgery on two to three procedures because remission was not achieved. Postoperative somatostatin receptor ligands (SRLs) were used by all patients. Six patients were treated with dopamine agonist in combination with SRL. Six patients (60%) received postoperative radiotherapy.

The mean follow-up period was 12.6±5.3 yrs (4-21 yrs). The mean GH and IGF-1 levels were 1.47±1.54 ng/mL (0.08-5.25) and 0.73±0.44 x ULN (0.08-1.56), respectively at the last visit. Residual adenoma was present at the last MRI in eight patients (mean diameter 9.0±3.6 mm). Panhypopituitarism rose from 10% at baseline to 30% at the last visit. During follow-up, one patient diagnosed breast cancer, while another diagnosed thyroid papillary cancer.

Giant GH-secreting pituitary adenomas can have a clinically aggressive behavior with mass effect. Moreover, treatment in patients with giant GH-secreting pituitary adenoma is complex and multimodal therapy is necessary.

Cardiovascular Endocrinology

PATHOPHYSIOLOGY OF CARDIOMETABOLIC DISEASE

Use of PCSK9 Inhibitors Post-Transplant

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Background:

Dyslipidemia is common in patients after transplant. While statins are the mainstay of therapy, interactions with immunosuppressants such as calcineurin inhibitors (CNIs) can limit dose titration or lead to intolerance of this important drug class. Withdrawal of statin therapy can precipitate hyperlipidemia and potentially accelerate cardiovascular disease in transplant recipients, including coronary allograft vasculopathy (CAV) in heart transplant (HT) patients. Proprotein convertase subtilisin-kexin type 9 inhibitors (PCSK9i) may provide a safe, effective option for such patients. PCSK9i profoundly reduce low-density lipoprotein (LDL) and subsequently the risk of cardiovascular events in nontransplant patients. Further, these novel agents have no known interactions with CNIs. There is a paucity of data describing PSCK9i use post-transplant, with only a few small case series reported in HT recipients. Here, we summarize our experience along with available literature on this topic.

Methods:

In this retrospective case series we investigated adult recipients of heart transplant who were treated with PCSK9 inhibitors from July 2015 to 2019 because of statin intolerance or refractory hyperlipidemia. We compared the data of patients at baseline and after various durations of therapy with the PSCK9i evolocumab and alirocumab using the median and interquartile range (IQR). Specifically, we evaluated PCSK9i efficacy, effect on immunosuppressant levels, cardiac function and adverse events.

Results:

Five patients (4 men; median age 54, IQR 52-60) underwent heart transplant an average of 7.4 years ago. Median treatment duration of evolocumab or alirocumab was 12 months (IQR 7-17). This led to a reduction of total cholesterol by 94 mg/dl (p=0.04) (47% decrease) and LDL cholesterol by 83 mg/dl (p=0.04) (69% decrease). No statistically significant difference in HDL cholesterol, triglycerides or liver function tests (LFTs) were observed. There were no episodes of rejection. Immunosuppressant levels remained at goal. One patient noted a few days of fatigue after alirocumab injections but otherwise no side effects were reported.

Conclusion:

The PCSK9 inhibitors evolocumab and alirocumab are promising alternatives to statin therapy in transplant recipients with statin intolerance or refractory hyperlipidemia. Our study showed their potential to significantly reduce LDL cholesterol in heart transplant patients without altering IST levels. No episodes of transplant rejection were noted.