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SAT-018

Polycystic ovary syndrome (PCOS) is a complex disorder characterised by endocrine, reproductive and metabolic abnormalities. Despite PCOS being the most common endocrinopathy affecting women of reproductive age, its etiology is poorly understood so there is no cure and symptom-oriented treatment is suboptimal. Elucidation of the underlying mechanisms involved in the pathogenesis of PCOS would pave the way for the development of new interventions for PCOS. Hyperandrogenism is the most consistent feature observed in PCOS patients, and recently aberrant neuroendocrine signalling and adipose tissue function have been proposed as playing a pathogenic role in the development of experimental PCOS. To investigate the role of adipose tissue and the brain as potential key sites for androgen receptor (AR)-mediated development of PCOS, we combined an adipocyte and brain-specific ARKO knockout (AdBARKO) mouse model with a dihydrotestosterone (DHT)-induced mouse model of PCOS. Wildtype (WT) and AdBARKO prepubertal mice were implanted with a blank or DHT implant and examined after 12 weeks. In WT control females, DHT exposure induced the PCOS reproductive traits of cycle irregularity, ovulatory dysfunction and reduced follicle health. In contrast, these reproductive features of PCOS were absent in DHT-treated AdBARKO females. The PCOS metabolic characteristics of increased adiposity, adipocyte hypertrophy and hepatic steatosis were induced by DHT in WT females. Despite DHT treatment, AdBARKO females displayed normal white adipose tissue weight, and adipocyte hypertrophy and hepatic steatosis were not evident. However, as with WT mice, DHT treatment induced increased fasting glucose levels in AdBARKO females. These results demonstrate that adipose tissue and the brain are key loci for androgen-mediated actions involved in the developmental origins of PCOS. These findings support targeting adipocyte and neuroendocrine AR-driven pathways in the future development of novel therapeutic strategies for PCOS.

Neuroendocrinology and Pituitary

NEUROENDOCRINE & PITUITARY PATHOLOGIES

Interleukin-2 Administration in Healthy Men Activates Cortisol Secretion in an Age-, Dose-, and Body Composition-Dependent Way.

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Context. Interleukin-2 (IL2), a proinflammatory cytokine, is used for treatment of malignancies. Increased cortisol and ACTH were noted, but not investigated in detail. This is the first study in healthy men which uses moderate high IL2 doses as used in cancer treatment.

Objective. The goal of this study was to quantify cortisol secretion after a single sc injection of IL2 at 1900 h in young and older healthy men in relation to dose, age and body composition. **Design.** This was a placebo-controlled, blinded, prospectively randomized cross-over study in 17 young subjects (mean age 24.1 yr, range 19–30 yr) and 18 older subjects (mean age 63.9 yr, range 60–75 yr). The subjects underwent 24 h of blood sampling at 10-min intervals, starting at 1800 h. At 2000 h IL2 (3 or 6 million units per m^2 body surface) or saline was injected sc. Lights were off between 2300 and 0700 h.

Setting. The study was performed in a Clinical Translational Research Unit.

Outcome measures. Mean concentrations of cortisol, deconvolution analysis, and approximate entropy. Abdominal visceral fat (AVF) and total abdominal fat (TAF) were calculated from single slice CT.

Results. Cortisol concentrations started to rise at 2300 h. The AUC's during the lights-on periods were unchanged by IL2. Therefore, most analyses were restricted to the 8 h lights-off period. In young volunteers pulsatile cortisol secretion increased from 52.9±5.8 to 77.0±8.0 µg/L/8h and in older subjects from 60.6±3.8 to 70.6±4.6 µg/L/8h (GLM: treatment P <0.0001, treatment x age: P=0.02, mean ± SEM). Thus, the effect was smaller in older subjects. Increasing the IL2 dose increased cortisol secretion in young subjects (P= 0.001), but not in older subjects (P=0.90). In addition, the slopes (mean ± SE) of the linear part of the concentration curves after IL-2 were steeper than after placebo, pointing to accelerated release (young 1.40±0.13 to 3.76±0.11, P<0.0001, in older 1.27±0.04 to 3.28±0.15, P<0.0001).The incremental nocturnal pulsatile cortisol secretion after IL2 was negatively related to body composition (AVF: R=–0.41, P=0.019; TAF R=–0.41, P=0.043). Nocturnal ApEn-cortisol did not increase after low dose IL2 (0.981± 0.099 to 0.991±0.046, P=0.92). After high-dose, ApEn increased from 0.877±0.041 to 1.024±0.049, P=0.008, not correlated with body composition, nor with age. The ApEn increase points to decreased secretory regularity imposed by enhanced CRF signaling, rather than diminished cortisol feedback, which leads to greater secretory regularity.

Conclusion. Il2, a paradigm for inflammation, increased pulsatile cortisol secretion, more in young than in older subjects. Higher IL2 doses in young subjects amplified cortisol secretion, but not in older subjects. Cortisol secretion exhibited an advance (earlier) time shift, accompanied by accelerated secretion. Incremental nocturnal cortisol secretion was negatively related to fat mass.

Neuroendocrinology and Pituitary

CASE REPORTS IN NEUROENDOCRINOLOGY BEYOND THE PITUITARY

SDHD Mutation: Nonfunctional Paragangliomas Presenting as Bilateral Carotid Body Tumors with Syncope

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