SAT-583

Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) is a peptide hormone known to regulate energy homeostasis[1]. Mice lacking PACAP are cold sensitive and have impaired adrenergic-induced thermogenesis[2-4]. Interestingly, *Pacap* null mice can survive cold housing if acclimated slowly, similar to what was observed in UCP1 deficient mice[4,5]. We hypothesized that *Pacap*-/- mice employ alternate thermogenic pathways to compensate for impaired adaptive thermogenesis and assessed shivering thermogenesis and UCP1-dependent and UCP1-independent adaptive thermogenesis in male and female *Pacap*-/- and *Pacap*+/+ with cold acclimation (4°C). Assessment of oxidative fibres in skeletal muscles and behavioural observations did not show evidence of prolonged shivering in male or female *Pacap*-/- mice during cold acclimation compared to *Pacap*+/+ mice. We did however observe morphological and molecular differences in adipose tissues of *Pacap*-/- mice compared to *Pacap*+/+ mice that were distinct in males and females. Cold-acclimated, female *Pacap*-/- mice had decreased induction of UCP1 protein in intrascapular brown fat (iBAT), yet had a significantly higher beiging and UCP1 immunoreactivity (ir) in gonadal white fat (gWAT) compared to female *Pacap*+/+ mice. Furthermore, beiging was observed in inguinal white fat (ingWAT) and gWAT of female *Pacap*-/- mice housed at thermoneutrality (30°C), a finding not observed in *Pacap*+/+ control mice. Unlike female mice, we did not observe impaired UCP1 induction in iBAT of male *Pacap*-/- mice compared to *Pacap*+/+ mice, and this was associated with negligible UCP1-ir in male gWAT similar to wildtype controls. Despite previous work that has established impaired adaptive thermogenesis in *Pacap*-/- mice[4], we show here that UCP1 protein can be induced in adipose tissues of *Pacap*-/- mice during cold acclimation, although to a lesser degree or in a different pattern compared to *Pacap*+/+ control mice. Taken together, this work suggests that while PACAP is clearly involved in regulating thermoregulation, it is not required for cold-induced UCP1 expression. In addition, this work highlights sexual dimorphism in adipose tissue remodeling and induction of thermogenesis with cold acclimation. References: (1) Rudecki AP, et al. Trends Endocrinol Metab. 2016;27(9), 620–632. (2) Gray SL, et al. J Mol Endocrinol. 2001;15(10), 1739–1747. (3) Gray SL, et al. J Endocrinol. 2002;143(10), 3946–3954. (4) Diané A, et al. J Endocrinol. 2014;222, 327–339. (5) Golozoubova V, et al. FASEB J. 2001;15, 2048–2050.

Adrenal

ADRENAL - TUMORS

Relationship Between Visceral Fat and the Position of Adrenal Glands in Cranial-Caudal Direction in Patients with Primary Aldosteronism

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SAT-177

Context: Adrenal glands locate at the retroperitoneal space and could be affected their positions by some factors. Adrenal glands being surrounded by visceral adipose tissue (VAT), we have hypothesized that the VAT amount influences the position of adrenal glands in cranial-caudal direction. In patients with primary aldosteronism (PA), comprehending the position of adrenal glands in cranial-caudal direction might be useful to predict the position of adrenal veins before performing adrenal venous sampling.
Objectives: To clarify the influence of VAT amount on the position of adrenal glands, we investigated the correlation of visceral fat parameters with the position difference of adrenal glands in cranial-caudal direction in patients with PA.
Materials and methods: This retrospective observational study included patients with PA according to the guidelines of both the Japan Endocrine Society and the Japan Society of Hypertension. Those with adrenal tumors more than 10 mm in diameter in computed tomography (CT) were excluded. We measured the position difference of the adrenal glands in cranial-caudal direction, from the top of right adrenal gland to the top of left adrenal gland by CT. We correlated visceral fat percentage (VF%), visceral fat area (VFA), and subcutaneous fat area (SCFA) evaluated by CT studies with the position difference of adrenal glands in cranial-caudal direction.
Results: We analyzed 150 patients [male (n = 50), female (n = 100)]. Patients' characteristics: Age was 54.8 ± 11.4, body mass index 24.9 ± 3.8 kg/m^2, plasma aldosterone concentration 133.5 [101–176] pg/ml, plasma renin activity 0.3 [0.2–0.5] ng/ml/h, VF% 25.8 [19.8–33.6] %, VFA 88.3 [60.9–125.0] cm^2, and SCFA was 147.4 [105.6–193.4] cm^2 (mean ± SD, or median [interquartile range]). The position difference of adrenal glands in cranial-caudal direction was 9.7 ± 10.0 mm. In 120 patients (80.0%), left adrenal glands locate at the upper position comparing to right adrenal glands. In 19 patients (12.7%), right adrenal glands were positioned at the upper comparing to left adrenal glands. A positive correlation of VF%, VFA with the position difference of adrenal glands in cranial-caudal direction were shown (r = 0.451, p < 0.001, r = 0.426, p < 0.001, respectively). No significant correlation of SCFA with the position difference of adrenal glands in cranial-caudal direction was shown (r = 0.122, p = 0.139). In patients with more VAT amount, right adrenal glands locate at the upper position comparing to left adrenal glands. In patients with less VAT amount, left adrenal glands locate at the upper position comparing to right adrenal glands.
Conclusions: Regardless of the variation of the position of adrenal gland on each side, the correlation was found between VAT and the position difference of adrenal glands in cranial-caudal direction in PA.

Neuroendocrinology and Pituitary

PITUITARY TUMORS: TRIALS AND STUDIES

Results From the Phase 3, Randomized, Double-Blind, Placebo-Controlled CHIASMA OPTIMAL Study of Oral Octreotide Capsules in Adult Patients with Acromegaly

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OR23-07

Many patients taking long-acting somatostatin receptor ligand (SRL) injections as first-line medical therapy in acromegaly report limitations, including ongoing disease symptoms especially near injection cycle end and injection site pain. Oral octreotide capsules may provide an alternative to monthly injections. The phase 3 Octreotide capsules versus Placebo Treatment In MultinationAL centers (OPTIMAL) study assessed efficacy and safety of oral octreotide capsules in patients with acromegaly controlled on injectable SRLs. A multinational, randomized, placebo-controlled study was conducted in 56 adult patients with active acromegaly. Eligible patients were ≥ 18 years of age, had evidence of active disease (IGF-I ≥ 1.3 x ULN ≥3 months after last pituitary surgery), and an average IGF-I ≤ 1.0 x ULN on a stable dose of SRL injections (octreotide or lanreotide). At baseline (1 month following the last injection), patients were randomized to receive octreotide capsule or placebo (28 per group) for 36 weeks, followed by an optional open-label oral octreotide extension. The primary endpoint was proportion of patients maintaining biochemical response, defined as IGF-I ≤ 1.0 x ULN (2-value average at weeks 34 and 36). Secondary endpoints included need for rescue with injectable SRLs, GH response (GH < 2.5 ng/mL), and time to loss of IGF-I response (IGF-I >1.0 and ≥ 1.3x ULN for 2 consecutive visits). Safety and tolerability were assessed. The primary endpoint was met, as 58% of patients receiving octreotide capsules maintained IGF-I response vs 19% receiving placebo (P=0.008). Mean IGF-I levels in patients receiving octreotide capsules were within the reference range at treatment end (0.97 x ULN) vs patients receiving placebo (1.69 x ULN). All secondary endpoints were met. Of patients receiving octreotide capsules, 75% completed 36 weeks without need for rescue therapy. However, 68% of the placebo group required rescue therapy. GH response was maintained at week 36 in a significantly larger proportion of patients receiving octreotide capsules than placebo (78% vs 30%; P=0.001). Median time to loss of IGF-I response was not reached by the end of the study for patients receiving octreotide capsules vs 16 weeks for the placebo group (P <0.0001). Five patients in the placebo group had IGF-I levels in the reference range at the end of 36 weeks. Only 2 (7% of placebo group) did not meet loss of response criteria anytime throughout the study. Octreotide capsules were safe and well tolerated; no new/unexpected safety signals were observed. Most patients (55/56) experienced at least one treatment emergent adverse event; most were mild or moderate in intensity. Overall, 90% of patients who completed the trial on octreotide capsules opted to enter the open label extension phase. These phase 3 data demonstrate octreotide capsules to be potentially safe and effective for the treatment of adults with acromegaly.

Reproductive Endocrinology

MALE REPRODUCTIVE CASE REPORTS

A Rare Case: Bone Pain and Continued Linear Growth in a Young Adult Male Due to Aromatase Deficiency

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SUN-033

Introduction:

Aromatase, the product of *CYP19A1*, catalyzes the conversion of androgens to estrogens. 46, XX infants with aromatase deficiency, due to androgen excess, present with ambiguous genitalia at birth. In 46, XY individuals, however, the subtle phenotypic features make the diagnosis even more difficult. Less than 15 male cases were reported in the literature and we present the first case of aromatase deficiency diagnosed in Taiwan.

Clinical Case:

A 23-year-old man, Burman overseas student of Chinese descent, presented to an orthopedist with a two-year history of left ankle pain, which was diagnosed as gout by his previous physician. Unexpectedly, unfused growth plates were discovered so he was referred to our pediatric endocrine clinic for evaluation. Reviewing his past history, we learned he is the third child of consanguineous parents. His mother experienced deepening of voice during this pregnancy which resolved following parturition. He was 177 cm tall at the age of 19. At the time he presented to our clinic, he weighed 95.3 kg and was 183 cm tall. Physical exam showed the ratio of U/L segment to be 0.82, stretched penile length 6.5 cm, bilateral testes > 25 mL, pubic hair at Tanner stage V, and presence of genu valgum. The skeletal age was 14 years and 6 months. Labs showed FSH 19.7 IU/L (0.7–11.1), LH 8.18 IU/L (0.8–7.6), total testosterone 1335 ng/dL (240–871), estradiol <20 pg/mL, DHEA-S 13.41 μmol/L (6.5–14.6), androstenedione 5.73 nmol/L (3.5–9.8) and 17-OH progesterone 6.55 nmol/L (2–10). GnRH (100 μg i.v) stimulation test showed a supranormal basal FSH level and a normal to higher LH response (FSH at baseline/peak were 23.0/38.6 IU/L; LH at baseline/peak were 8.81/47.7 IU/L). Under the clinical suspicion of aromatase deficiency, we performed genetic sequencing of *CYP19A1* (NM_031226) and found a homozygous missense variant c.1108G>A (V370M), a previously reported pathogenic mutation.

A diagnosis of aromatase deficiency was made. He also had hypertension (156/87 mmHg), dyslipidemia (T-cholesterol 236 mg/dL, LDL-C 175 mg/dL) and insulin resistance (AC glucose 87 mg/dL, insulin 23.5 μU/mL, HOMA-IR 5.0, Hb1Ac 5.6%). Bone mineral density of lumbar spine (DXA) showed a T-score of -2.8, consistent with the diagnosis of osteoporosis.

Conclusion:

Estrogen is pivotal for epiphyseal closure in both sexes. As demonstrated in this case, estrogen deficiency in men results in tall stature and eunuchoid habitus, while it is also associated with low bone density and metabolic syndrome. The gonadotropin response in this report suggests