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ENDOCRINE SOCIETY

Genetics and Development (including Gene Regulation)

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

Identification of Membrane Proteins That Enhance the Responsiveness of the Ghrelin Receptor

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OR24-02

Ghrelin, a 28-amino acid peptide gut hormone, occurs in acylated (AG) and unacylated (UAG) variants. AG is a GH secretagogue as well as being orexigenic and diabetogenic, acting via the growth hormone secretagogue receptor (GHSR1a) in the hypothalamus and pituitary. UAG counteracts these metabolic effects through unknown mechanisms. While screening for potential UAG receptor(s) we discovered previously uncharacterised interactions of AG and UAG with five cell membrane proteins (MPs), three of which are known to modulate metabolism. Here, we studied if two of these MPs (MP1 & 2) could modulate GHSR1a signalling by expressing their transgenes in HEK293 cells. As GHSR1a is coupled with calcium signalling via Gq proteins, aequorin luminescence was used to evaluate Ca^{2+} influx into the cells. Transfected cells were treated with either AG, UAG, or soluble parts of the MPs, or combinations thereof.

MP2 markedly enhanced the efficacy (~5.5-fold), but not the potency, of AG-induced Ca^{2+} influx, whereas MP1 had no effect on Ca^{2+} influx. Neither MP1 nor MP2 overexpression altered cellular GHSR1a levels. In the absence of GHSR1a, MP2 was unable to stimulate an AG-induced Ca^{2+} influx. UAG treatment (100nM) had no effect on GHSR1a-mediated Ca^{2+} influx in the presence or absence of MP2. MP2 is post-translationally modified and we suspected this to be important for its activity. However, removal or blockade of these modifications had no effect on the ability of MP2 to enhance GHSR1a signalling. Moreover, incubating the cells with soluble ectodomain of MP2 did not alter its effect on GHSR1a signalling. Nevertheless, induction of ectodomain shedding with PMA (0.4-1μM) dose-dependently reduced the AG-induced Ca^{2+} response to 0.5-0.2 of control levels (DMSO) in MP2-GHSR1a co-transfected cells. Unlike MP2, which has a transmembrane and intracellular domain, MP1 is attached to the plasma membrane via a glycosylphosphatidylinositol (GPI) anchor and lacks an intracellular domain. Since MP1 is otherwise structurally similar to MP2, we suspected that the intracellular domain of MP2 may be important for its function. Therefore, we expressed chimeras of MP2 and MP1 in which the GPI linkage site and the transmembrane/intracellular domains were exchanged. The MP2 ectodomain with a GPI-anchor had similar stimulatory effects on GHSR1a signalling as full-length MP2, whereas the MP1 ectodomain with MP2 transmembrane and intracellular domain only enhanced GHSR1a signalling by approximately 3-fold.

In conclusion, we have identified a membrane protein as a novel component of the ghrelin signalling pathway that markedly enhances the response of the ghrelin receptor to AG. Our current data suggest its ectodomain is important in mediating this effect. Studies are ongoing to fully delineate the mode of interaction and to determine the role of MP2 in ghrelin signalling *in vivo*.

Reproductive Endocrinology

MALE REPRODUCTIVE HEALTH - FROM HORMONES TO GAMETES

Low Serum Testosterone (T) Is Associated with Poor Health Status in Young to Middle-Aged Human Immunodeficiency Virus (HIV)-Infected Men

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SAT-050

BACKGROUND: The relationship between health status, defined by frailty and comorbidities, and serum T levels has been widely demonstrated in general population, while only one previous retrospective study has explored it in HIV-infected men[1].

AIM: To investigate the association between frailty and gonadal status by assessing serum total T (TT) with Liquid Chromatography tandem Mass Spectrometry (LC-MS/MS) in a cohort of HIV-infected men.

METHODS: Prospective, cross-sectional, observational study on HIV-infected men (age <50 years) with ongoing Highly Active Antiretroviral Therapy. Serum TT was assessed by the gold standard ID-LC-MS/MS. Sex hormone-binding globulin (SHBG) was measured by chemiluminescent immunoassay. Calculated free T (cFT) was obtained by Vermeulen equation. Multimorbidity was defined as at least 3 comorbid conditions, including: hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, osteoporosis, chronic viral hepatitis and cancers. Frailty was calculated through the validated 37-item frailty index (FI)[2]. Patients with FI>0.21 were considered frail. ***Statistical analysis:*** Mann-Whitney *U* test was used to compare continuous variables. Correlations were performed using linear regression models.

RESULTS: 315 consecutive HIV-infected men were enrolled (mean age 45.3±5.3 years; average duration of HIV-infection 16.3±8.8 years). 128 patients (40.5%) were comorbid and 207 (64.9%) were frail. Either cFT (p=0.001) or TT (p<0.001) were lower in comorbid patients than others. FT was inversely related to the number of comorbidities (p<0.001, R^2=0.045). Accordingly, cFT (p=0.003) and TT (p<0.001) were significantly lower in frail patients.

Frailty score was inversely correlated with cFT (p<0.001, R^2=0.058), TT (p=0.041, R^2=0.014) and SHBG (p=0.003, R^2=0.029). However, after adjustment for age and duration of HIV-infection, cFT, TT and SHBG were excluded from the regression model.

CONCLUSIONS: Low cFT and TT levels are associated with multimorbidity and poor health status in HIV infected men. The bidirectional nature of this relationship leads to the figuration of an intriguing vicious circle where T deficiency triggers the onset of comorbidities or, vice versa, poor health status induces hypogonadism. At the same time, notwithstanding the inverse relation between FT and frailty, it seems that other stronger predictive factors, and in particular the duration of infection, are involved in determining the health outcome in this clinical setting.

REFERENCES

[1]Rochira V *et al*. Low testosterone is associated with poor health status in men with human immunodeficiency virus infection: a retrospective study. *Andrology*. 2015 Mar;3(2):298-308.

[2]Guaraldi *et al*. A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity. *AIDS*. 2015 Aug 24;29(13):1633-41.

Adrenal

ADRENAL CASE REPORTS I

Treatment-Resistant Hypertension in a Post-Transplant Patient with Cystic Fibrosis: A Rare Case of Pheochromocytoma

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SAT-209

Background: Pheochromocytoma is a rare catecholamine-producing tumor with an estimated incidence of less than 0.1% in the global population. We present the case of a pheochromocytoma in a 25-year-old man with a background history of a double-lung transplant for Cystic Fibrosis, carried out 5 years earlier. **Clinical Case:** A 25 year old, with a background history of Cystic Fibrosis and a Double Lung transplant in 2012 presented to the emergency department with crampy abdominal pain, nausea and vomiting. He was diagnosed with Distal Intestinal Obstruction syndrome (DIOS) for which he was admitted for rehydration and laxatives. Contrast-enhanced computed tomography (CT) imaging of the abdomen and pelvis which showed a 3.4 cm right adrenal lesion, which was confirmed by a subsequent MRI Adrenals and an Endocrinology review was requested. On review, the patient was noted to be hypertensive with a blood pressure averaging 170/90 despite treatment with 3 different anti-hypertensive medications - namely amlodipine, telmisartan and doxazosin. On review of his medical notes, it was clear that he had been persistently hypertensive over the last 3 years. On further questioning, he noted increasingly frequent sweating episodes over the last number of months but denied any palpitations, headache or back pain. Laboratory analysis showed an elevated plasma normetanephrines (NMN) of 3167 pmol/L (182-867) as well as elevated metanephrines (MN) of 793 pmol/L (61-377) and high 3-MT of 257 pmol/L (<185). His MIBG scan showed only a mild increase in the uptake of tracer to the right adrenal gland compared to the left. The case was discussed at a multidisciplinary meeting and given the suggestive laboratory and radiologic findings, a presumptive diagnosis of pheochromocytoma was made. After controlling blood pressure with an alpha-blocker and beta-blocker for a week, the patient was hydrated and scheduled for an elective right adrenalectomy. The histopathology of the excised adrenal gland was consistent with a 3cm pheochromocytoma with none of the adverse features associated with malignant potential. The patient recovered well post-op, his blood pressure normalised and he was discharged home well for follow-up at the Endocrine and Transplant clinics. **Conclusion:** We describe a rare case of a right adrenal pheochromocytoma in a young man with multiple co-morbidities, who completely recovered after tumor resection. This case highlights the crucial importance of investigating secondary causes of hypertension, especially in younger patients. This is the first documented case in the literature of a case of pheochromocytoma in a post-transplant patient with Cystic Fibrosis. ***References:*** 1. Farrugia FA, Marikos G et al. Pheochromocytoma, diagnosis and treatment: Review of the literature. Endocrine Regulation, Volume 51, Issue 3, 30th August 2017.

Adrenal

PROGRESS IN ADRENAL CORTEX AND MEDULLA RESEARCH

NAD+ Availability Modulates 11β-HSD1-Mediated Glucocorticoid Regeneration in Mouse Skeletal Muscle

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OR03-06

11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an NADPH-dependant reductase located in the sarcoplasmic reticulum (SR) lumen of skeletal muscle. It generates active glucocorticoids to regulate permissive and adaptive metabolism and contributes to the development of the Cushing's syndrome phenotype in mice receiving oral corticosterone. The SR enzyme hexose-6-phosphate dehydrogenase (H6PDH) generates NADPH which supports 11β-HSD1 activity. H6PDH depletion disrupts the SR NADPH/NADP ratio leading 11β-HSD1 to assume glucocorticoid-inactivating dehydrogenase activity. Little is understood regarding routes to NAD(P)(H) biosynthesis and metabolism in the SR. Here we asked whether modulating cellular nicotinamide adenine dinucleotide (NAD+) availability (the parent molecule of NAD(P)(H)) would influence muscle 11β-HSD1 activity given its sensitivity to the SR