Adrenal Physiological and Disease

Active Steroid Hormone Synthesis Renders Adrenocortical Cells Highly Susceptible to Type II Ferroptosis Induction

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SUN-211
Context: Cell death in the adrenal cortex is ill understood but of high clinical relevance. Resistance of adrenocortical carcinoma (ACC) to current treatment with mitotane and chemotherapy calls for an improved understanding of adrenal cortical cell death processes. Ferroptosis is an iron-dependent form of regulated cell death which is characterized by polyunsaturated lipids in adenoma (AdA) and arachidonic acid (AA) peroxidation. Aim: To address the potential role of ferroptosis in the adrenal gland as a potential treatment target of ACC. Methods: Human ACC cells H295R, CU-ACC1 and 2 were used. Protein expression of key enzymes was determined by western blotting. Lipid peroxidation was quantified with BODIPY 581/591 and cell viability with CellTiterGlod after treatment with known inducers and inhibitors of ferroptosis and steroidogenesis, respectively. Results: Adrenocortical tissues are enriched in AdA and AA and express high levels of genes relevant to ferroptosis, such as glutathione peroxidase 4 (GPX4) and long-chain-fatty-acid CoA ligase 4 (ACSL4). Inhibition of GPX4 with RSL3 led to cell death in H295R, CU-ACC1 and 2 cells at EC50 values of 2.4x10-7, 8.1x10-7 and 1.5x10-5M, respectively. The steroidogenesis inhibitor ketoconazole completely reversed RSL3 cytotoxicity in all three steroidogenic cell lines by reducing lipid peroxidation. Mitotane induced lipid peroxidation but inhibition of ferroptosis with liproxstatin did not protect mitotane-induced cell death. Conclusion: Adrenocortical cells are highly sensitive to ferroptosis due to active steroidalogenesis. Triggering this form of cell death could present future novel treatment options against ACC.

Cardiovascular Endocrinology

Pathophysiology of Cardiometabolic Disease

The Crosstalk Between Central Leptin and PPARbeta/delta Protects the Heart Against Oxidative Stress Damage and the Development of Hypertrophy

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SUN-570
Cardiovascular disease is a common cause of morbidity and mortality in obese people with type 2 diabetes, which is often associated with increased levels of leptin. While many studies hint at the existence of important roles for both hyperleptinemia and leptin resistance in obesity and diabetes-associated cardiovascular disease, others support that leptin has cardioprotective effects. Leptin action comprises direct effects on cardiac tissue and indirect effects mediated via the sympathetic nervous system. Since the molecular underpinnings of leptin-regulated pathways in cardiac tissue in normoleptinemic animals remain less well defined, we addressed the effects of central leptin infusion on cardiac function and remodeling analyzing FOXO1/3 and mTORC1 pathways, paying special attention to PPARβ/δ as a key leptin signal regulator. We found that central leptin regulated dynamically the network between PPARβ/δ, FOXOs, and mTORC1 in cardiac tissue, through antioxidant, thermogenic and autophagy programs. Intracerebroventricular (ICV) leptin infusion (0.2μg/day) for 7 days in male 3-months-old Wistar rats induced protection from hypertrophy without increasing TBARS and protein carbonylation nor ROS/RSN cardiac levels. These effects were further supported by both increased of Sod2 and Ucp1 expression and reduced Tgf-α. Atrophy-related ubiquitin ligase Atrogin-1, accompanied by Beclin-1 and LC3II, gene products of the autophagic pathway response, were all upregulated by central leptin. In addition, mTORC1 activity and OXPHOS protein levels were decreased without affecting cellular function. Moreover, the content of carbonylated proteins did not increase upon the central leptin treatment, suggesting a key role of leptin in preventing cardiac oxidative stress. Finally, the pharmacological inhibition of PPARβ/δ, via in vivo administration of the selective antagonist GSK0660, blunted the induction of FOXO1/3 and Atrogin-1 in the heart mediated by icv leptin infusion. Together these data support that PPARβ/δ may act as a mediator of central leptin effects on cardiac cellular reprogramming through the activation of FOXO1/3 and the inactivation of mTORC1 pathways, and the upregulation of Atrogin-1 and the genes involved in energy uncoupling.

Neuroendocrinology and Pituitary Tumors II

Management and Therapeutic Response Comparison in Prolactinomas According to Tumor Size

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MON-324
Management and Therapeutic Response Comparison in Prolactinomas According to Tumor Size

Prolactinomas are the most common type of functioning pituitary adenomas and up to 50% of all adenomas in clinical practice. Prolactinomas are more prevalent in women; nonetheless, they may occur at any age and in both genders, and represent the most common cause non-physiological hyperprolactinemia. Prolactin-secreting adenomas are classified by their tumor size as follows:

- Microadenomas: <1 cm
- Small adenomas: 1-2 cm
- Large adenomas: >2 cm

The size of prolactinomas can impact the management and therapeutic response. In general, microadenomas are managed conservatively with bromocriptine, while larger adenomas may require surgical intervention or other therapies. The management of prolactinomas is guided by their size, as well as the presence of symptoms and the risk of complications such as visual field defects or optic nerve compression.
and further demonstrated elevated GnRHR-autoantibody releasing hormone receptor (GnRHR) in PCOS patients, ward the second extracellular loop (ECL2) of gonadotropin-ovary and so on. We previously showed reported a high percentage of activating autoantibodies (AAb) directed to ovarian tissues between two groups. Conclusion: Chronic GnRH-AAb (GnRHR-AAb) could induced insulin resistance in energy storage and peripheral tissue in immunized animals. In the present study, we have now induced specific GnRHRL-directed AAb in rats and explored the underlying mechanisms of their resultant reproductive dysfunction. Methods: Sixteen SD rats were randomly divided into 2 groups: a GnRH group (n=8) and a control group (n=8). Rats in the GnRH group were immunized with GnRHR ECL2 peptide while the controls were not. Epitope mapping of GnRHR-ECL2-directed AAb was performed using octapeptide multipin solid-phase peptides. Rat estrus cycle was measured through pudendum appearance and vaginal smears. Ovarian and pituitary tissues were collected to observe ovarian morphological changes, to examine the expressions of proteins and genes of insulin signaling pathway by Quantitative real-time PCR respectively. The concentration of inflammatory cytokines in the ovary was detected by Bioplex Pro™ magnetic bead-based assays on the Bio-plex®. Results: The GnRHR-AAb titers and activity in the GnRH group were significantly higher than the control group, and the GnRHR-AAb from the immunized rats reacted predominantly with the peptide sequence FSQCVTHC of the GnRHR-ECL2. Numbers of LH pulses and concentration of testosterone in GnRHR group were significantly higher than control group. The GnRH group exhibited lower frequency of in the appearance of proestrus and estrous phases while the control group represented had a higher frequency in the appearance of metestrus and diestrus stages on estrus cyclicity. The GnRH-immunized group showed demonstrated increased atretic follicles, decreased corpora lutea, loosely packed granulosa cells, and thecal cell hyperplasia in ovarian tissue compared with controls group. There was GnRH group represented increased expressions of IRS-1, P13K and GLUT-1 in ovarian and pituitary tissues compared with control group. However, no obvious changes of inflammatory cytokines are observed in ovarian tissues between two groups. Conclusion: Chronic elevated GnRHR-AAb exerts induced reproductive dysfunction through increased ovarian LH secretion and androgen production, thus likely leading to compensatory hyperinsulinemia which ultimately enhanced insulin signaling in reproductive tissues to exert more and androgen production to, which may provide a novel etiological mechanism for PCOS.

Reproductive Endocrinology

FEMALE REPRODUCTION: BASIC MECHANISMS

The Effect of GNRHR Autoantibody on Reproduction Function and Insulin Signaling Intermediates in a New Animal Model of Polycystic Ovary Syndrome

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Background: Polycystic ovary syndrome (PCOS), a metabolic and reproductive associated disease, defined as hyperandrogenism with reproductive dysfunction including menstrual disorder, anovulation, infertility, polycystic ovary and so on. We previously showed reported a high percentage of activating autoantibodies (AAb) directed toward the second extracellular loop (ECL2) of gonadotropin-releasing hormone receptor (GnRHR) in PCOS patients, and further demonstrated elevated GnRHR-autoantibody

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS I

Posterior Reversible Encephalopathy Syndrome Associated with Malignant Hypercalcemia and Hypertension Due to Primary Hyperparathyroidism

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SAT-378

Posterior Reversible Encephalopathy Syndrome associated with malignant hypercalcemia and hypertension due to primary hyperparathyroidism

Background

Posterior Reversible Encephalopathy Syndrome (PRES) is an acute neurological entity characterized by headache, altered mental status, visual loss and seizures. It can be