Adrenal

ADRENAL PHYSIOLOGY AND DISEASE

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

Isabel Weigand, PhD[1], Jochen Schreiner, Mr[1], Florian Roehrig, PhD[2], Na Sun, PhD[3], Landwehr Laura-Sophie, Ms[1], Hanna Urlaub, Ms[1], Katja Kiseljak-Vassiliades, MD[4], Margaret E. Wierman, MD[4], José Pedro Friedmann Angeli, PhD[2], Axel K. Walch, MD[3], Silviu Sbiera, PhD[1], Martin Fassnacht, MD[1], Matthias Kroiss, MD, PhD[1].

[1]University Hospital Wuerzburg, Wuerzburg, Germany, [2]University of Wuerzburg, Wuerzburg, Germany, [3]Helmholtz Center Munich, Munich, Germany, [4]University of Colorado School of Medicine, Aurora, CO, USA.

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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 adrenic (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 CellTiterGlo 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 EC_{50} values of $2.4x10^{-7}$, $8.1x10^{-7}$ and $1.5x10^{-8}$ M, 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 steroidogenesis. 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

BLANCA M. RUBIO, predoctoral student, CRISTINA MORA, PhD, LORENA MAZUECOS, predoctoral student, CRISTINA PINTADO, PhD, CARMEN ARRIBAS, PhD, Antonio Andres, PHD, NILDA GALLARDO, PhD.

UNIVERSIDAD DE CASTILLA-LA MANCHA, Ciudad Real, Spain.

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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 *Tnf-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

PITUITARY TUMORS II

Management and Therapeutic Response Comparison in Prolactinomas According to Tumor Size

Romina Flores-Cardenas, MD.

INSTITUTO NACIONAL DE CIENCIAS, Ciudad de Mexico, Mexico.

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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: