Steroid Hormones and Receptors

STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

Deletion of Nuclear Receptor Constitutive Androstanse Receptor CAR Increases Anxiety and Lowers Androgen Levels

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The orphan nuclear receptor, Constitutive Androstane Receptor (CAR, NR1I3) is primarily known to regulate the transcriptional networks involved in detoxification. We have identified a novel extra-hepatic role of CAR in the transcriptional networks involved in detoxification. We have identified a novel extra-hepatic role of CAR in regulating androgen levels and modulating testis function. Previous data has revealed that CAR activation by estradiol and inactivation by androstanol suggests an intricate link between sex hormones and CAR. We investigated control wild type and CARKO mice and found that the serum testosterone and androstenedione levels were lower in the absence of CAR. As expected, we did not find any induction of the genes in the detoxification machinery including, Cyp3a, Cyp2b, Cyp2c family, Sult2a1 and Mrp. The decrease in the androgen levels in the CARKO mice is consistent with decrease in the anogenital distance, increased anxiety as measured by marble burying and elevated plus maze but no change in testis weight. H&E staining of CARKO mice shows accumulation of fat in the Leydig cells and lower numbers of Leydig cells which are in accordance with the loss of androgen levels. In addition, we will examine the consequence of reduced androgen and the hypothalamic-pituitary-gonadal axis in the CARKO mice.

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DHT Causes Liver Steatosis via Transcriptional Regulation of SCAP in Lean female Mice

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Hyperandrogenemia (HA) and insulin resistance are hallmarks of polycystic ovary syndrome (PCOS). These hallmarks are also integral elements of non-alcoholic fatty liver disease (NAFLD). Administering low dose dihydrotosterone (DHT) induced a lean PCOS-like female mouse model. The molecular mechanism of HA-induced NAFLD has not been determined. We hypothesized that low dose DHT would interrupt hepatic lipid metabolism leading to NAFLD. We extracted white adipose tissue (WAT), liver, and skeletal muscle from control and low dose DHT female mice; and performed histological and biochemical lipid profiles, Western blot, immunoprecipitation, chromatin immunoprecipitation, and real-time quantitative PCR analyses. DHT lowered the 65 kD form of cytosolic SREBP1 in the liver and WAT compared to controls. However, DHT did not alter the levels of the active and inactive forms of SREBP2 in the liver and WAT. DHT increased SCAP protein expression and SCAP-SREBP1 binding via AR binding to intron-8 of SCAP leading to increased SREBP1 in liver and WAT compared to controls. However, DHT did not alter the levels of the active and inactive forms of SCAP. The decrease in the 65 kD form of cytosolic SREBP1 in the liver and WAT. DHT increased SCAP protein expression and SCAP-SREBP1 binding via AR binding to intron-8 of SCAP leading to increased SREBP1 in liver and WAT. DHT increased SCAP protein expression and SCAP-SREBP1 binding via AR binding to intron-8 of SCAP leading to increased SREBP1 in liver and WAT. DHT increased SCAP protein expression and SCAP-SREBP1 binding via AR binding to intron-8 of SCAP leading to increased SREBP1 in liver and WAT. DHT increased SCAP protein expression and SCAP-SREBP1 binding via AR binding to intron-8 of SCAP leading to increased SREBP1 in liver and WAT. 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Epitranscriptomic Reader HNRNPA2B1 Confers Endocrine Resistance to Breast Cancer Cells

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Despite new combination therapies improving survival of breast cancer patients with estrogen receptor α (ER+) tumors, the molecular mechanisms for endocrine-resistant metastatic disease remain unresolved. HNRNPA2B1...
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Estrogen Receptor Alpha Is Required to Protect Daily Metabolic Rhythms From Disruption by High-Fat Feeding in Female Mice

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The circadian system is a critical regulator of obesity in male mice, but its role in females is poorly understood. In our previous studies we found that estrogen regulates daily rhythms in female mice to confer resistance to diet-induced obesity, but the mechanism is unknown. Estrogen signals via the classical estrogen receptor alpha (ERα) to regulate metabolism and obesity. Therefore, in this study we tested the hypothesis that estrogen regulates daily metabolic rhythms in females via ERα. To do so, we studied daily rhythms in female global ERα knockout (ERα KO) with the circadian reporter, PERIOD2::LUCIFERASE, fed high-fat diet for 6 weeks. ERα KO female mice became obese and hyperglycemic when fed high-fat diet, while wild-type females were resistant to diet-induced obesity. Chronic high-fat diet feeding also reduced the amplitude of the daily rhythm of eating behavior in ERα KO, but not wild-type, female mice. In wild-type females, the amplitude of the locomotor activity rhythm increased during high-fat feeding. In contrast, high-fat feeding decreased the amplitude of the activity rhythm in ERα KO females. The temporal relationship between central and peripheral circadian tissue clocks was disrupted by high-fat feeding in ERα KO females since the phase of the liver PERIOD2::LUCIFERASE rhythm was advanced 4 hours by high-fat feeding in ERα KO mice compared to wild-type females. Taken together these results show that estrogen signals via ERα to protect daily metabolic rhythms from disruption by high-fat feeding in female mice.

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Glucocorticoid Mediated Transcriptional Activity in Human Corneal Epithelial Cells Lacking the Glucocorticoid Receptor

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The cornea is the dome-shaped transparent outermost layer of the eye, forming a physical barrier to protect the internal structures of the eye. Glucocorticoids are a mainstay in the treatment of ophthalmic diseases for their anti-inflammatory and anti-angiogenic properties. However, high doses or chronic use of glucocorticoid therapy can lead to vision-impairing effects such as increase in intraocular pressure and the formation of cataracts. The exact signaling pathways responsible for these undesirable effects of glucocorticoid use is poorly understood. One of the major molecular actions of glucocorticoids is to regulate transcription through its cognate nuclear receptor, the glucocorticoid receptor. We have previously reported the effect of glucocorticoids on global gene expression and their role in wound healing and barrier function in immortalized human corneal epithelial cells (HCE-T). In the current study, we knocked down glucocorticoid receptor using siRNA (GRKD) to determine the function of the glucocorticoid receptor in HCE-T cells. Successful knockdown of glucocorticoid receptor was confirmed by RT-PCR and immunoblot experiments. Genome-wide microarray analysis was performed and an FDR adjusted p value less than 0.01 was considered the cut off to create the list of differentially expressed genes (DEGs). Comparison of GRKD cells to HCE-T cells expressing endogenous glucocorticoid receptor (referred as NTC for No Target Control siRNA) revealed that expression of 2150 genes was altered in HCE-T cells when glucocorticoid receptor was knocked down, indicating that glucocorticoid receptor in corneal epithelial cells regulates a large cohort of genes. Inhibition of matrix metalloproteases, granulocyte adhesion and diapedesis, cyclins and cell cycle regulation were the top canonical pathways predicted by Ingenuity Pathway Analysis (IPA) to be altered in GRKD cells. In a 6-hour treatment with dexamethasone (Dex), a synthetic