this result, genetic deletion of NFATc4 reduced the basal expression of CYP11B2 and impaired the $K^+$-stimulated expression of this gene. Conversely, the expression of a constitutively active form of NFATc4 drastically increased the expression of CYP11B2 in NCI-H295R cells which remained unaltered upon treatment with $K^+$ or tacrolimus. Finally, preliminary experiments using ZG-CnB1-KO mice suggest that Cn deletion in the ZG blunts the increase in aldosterone excretion triggered by high $K^+$ diet. Altogether, our data indicate that Cn function is indispensable for the physiological regulation of aldosterone production. Moreover, Cn may represent a novel molecular target for the pharmacological treatment of primary aldosteronism.

## Steroid Hormones and Receptors
### STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

***Carbonyl Reductase 1 Overexpression in Adipose Amplifies Local Glucocorticoid Action and Impairs Glucose Tolerance in Lean Mice***

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Glucocorticoids play a critical role in metabolic homeostasis. Chronic or excessive activation of the glucocorticoid receptor (GR) in adipose tissue contributes to metabolic disorders such as glucose intolerance and insulin resistance. Steroid-metabolising enzymes in adipose, such as 11β-HSD1 or 5α-reductase, modulate the activation of GR by converting primary glucocorticoids into more or less potent ligands. Carbonyl reductase 1 (CBR1) is a novel regulator of glucocorticoid metabolism, converting corticosterone/cortisol to 20β-dihydrocorticosterone/cortisol (20β-DHB/F); a metabolite which retains GR activity. CBR1 is abundant in adipose tissue and increased in obese adipose of mice and humans[1] and increased Cbr1 expression is associated with increased fasting glucose[1]. We hypothesised that increased Cbr1/20β-DHB in obese adipose contributes to excessive GR activation and worsens glucose tolerance. We generated a novel murine model of adipose-specific *Cbr1* over-expression (R26-Cbr1Adpq) by crossing conditional knock-in mice with Adiponectin-Cre mice. CBR1 protein and activity were doubled in subcutaneous adipose tissue of male and female R26-Cbr1Adpq mice compared with floxed controls; corresponding to a two-fold increase 20β-DHB (1.6 vs. 4.2ng/g adipose; P=0.0003; n=5-7/group). There were no differences in plasma 20β-DHB or corticosterone. Bodyweight, lean or fat mass, did not differ between male or female R26-Cbr1Adpq mice and floxed controls. Lean male R26-Cbr1Adpq mice had higher fasting glucose (9.5±0.3 vs. 8.4±0.3mmol/L; P=0.04) and worsened glucose tolerance (AUC 1819±66 vs. 1392±14; P=0.03). Female R26-Cbr1Adpq mice also had a worsened glucose tolerance but fasting glucose was not altered with genotype. There were no differences in fasting insulin or non-esterified fatty acid between genotypes in either sex. Expression of GR-induced genes *Pnpla2*, *Gilz* and *Per1*, were increased in adipose of R26-Cbr1$^{Adpq}$ mice. Following high-fat diet induced obesity, no differences in bodyweight, lean or fat mass, with genotype were observed in male and female mice, and genotype differences in fasting glucose and glucose tolerance were abolished. In conclusion, adipose-specific over-expression of *Cbr1* in lean male and female mice led to increased levels of 20β-DHB in adipose but not plasma, and both sexes having worsened glucose tolerance. The influence of adipose CBR1/20β-DHB on glucose tolerance was not associated with altered fat mass or bodyweight and was attenuated by high-fat diet-induced obesity. These metabolic consequences of Cbr1 manipulation require careful consideration given the wide variation in CBR1 expression in the human population, the presence of inhibitors and enhancers in many foodstuffs and the proposed use of inhibitors as an adjunct for cancer treatment regimens. **Reference:** Morgan et al., Scientific Reports. 2017; 7.

## Steroid Hormones and Receptors
### STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

***Chronic Dexamethasone Treatment Leads to Less Weight Gain and Ameliorated Glucose Tolerance in Mice; Role of the Cytoprotective Nrf2 Pathway***

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**Introduction:** Chronic glucocorticoid administration is necessary in a variety of conditions including but not limited to autoimmune, inflammatory and cancer-related diseases in order to relieve symptoms and sustain disease progression. However, there are adverse effects that include increase in glucose levels and others whose severity depends on the dose and duration of glucocorticoid exposure. It has been described that dexamethasone induces oxidative stress in cells by increasing reactive oxygen species (ROS) and this is one of the causes of insulin resistance at the cellular level. Nrf2 is a transcription factor which co-ordinates the antioxidant response and its activation has been shown to ameliorate insulin resistance in murine models. **Hypothesis**: We hypothesized that deletion of Nrf2 will lead to a more glucose intolerant insulin resistant phenotype in mice chronically treated with dexamethasone as cells would be exposed to higher ROS levels. **Methods:** To this end, 3-months old wild-type (WT) and Nrf2 knockout (KO) C57BL6J mice were treated intraperitoneally with 2 mg/kg dexamethasone or saline 3 times per week for 3 months. 5-10 mice were included per genotype per treatment and both male and female mice were used. Weekly measurements of body weights were performed and intraperitoneal glucose tolerance tests were done on the second and third month of treatment. Mice were sacrificed

24 hours after the last dose of dexamethasone and blood, white adipose tissue, soleus muscle and liver were collected for RNA preparation and quantitative RT-PCR analysis. Quantitative analysis of trabecular bone parameters was performed by micro-CT. **Results:** Both male and female mice treated with dexamethasone gained less weight over time and surprisingly were more glucose tolerant than the control group. Absence of Nrf2 did not seem to considerably affect the body weight but KO mice tended to have lower body weights after dexamethasone treatment in both genders with the effect on male mice being statistically significant (25% lower, $p<0.05$). Surprisingly, both WT and KO mice of both genders showed lower fasting blood glucose levels after 3 months of treatment and better glucose tolerance. Livers of KO mice showed lower levels (~50%) of the cytoprotective genes Nqo1 and Gclc as expected but no difference was observed after dexamethasone treatment. Sarcopenia muscle markers Mafbx1 and Murf1 showed no significant changes. Male mice showed increased expression of Pnpla3 in white adipose tissue indicating increased lipolysis upon dexamethasone exposure. Micro-CT showed minor changes in the bone parameters without difference between male WT and Nrf2KO mice. **Conclusions:** Dexamethasone unexpectedly led to better glucose tolerance and lower body weight which is uncommon in humans but it has been described previously in mouse models. More analyses are in progress to fully elucidate this phenotype.

## Steroid Hormones and Receptors

### STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

***Deletion of Nuclear Receptor Constitutive Androstane 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 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 hypothalamus-pituitary-gonadal axis in the CARKO mice.

## Steroid Hormones and Receptors

### STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

***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 (NALFD). Administering low dose dihydrotestosterone (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 SCAP mRNA. FAS mRNA and protein expression was increased in liver of DHT mice. p-ACC levels were unaltered in liver but decreased in WAT. Other lipid metabolism pathways were examined in liver and WAT, but no changes were observed. Our findings suggest that DHT increased de novo lipogenic proteins resulting in increased NAFLD via regulation of SREBP1 in liver. We show that in the presence of DHT the SCAP-SREBP1 interaction is elevated leading to increased nuclear SREBP1 resulting in increased de novo lipogenesis. We propose that the mechanism of action is increased AR binding to an ARE in SCAP intron-8.

## Steroid Hormones and Receptors

### STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

***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