lack of knowledge. The health team should be trained and the approach should consider the mothers' perspectives and be appropriate to the cultural context. Educational actions may improve understanding and reduce the DSD stigma.

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

Betamethasone Induces a Unique Transcriptome in Neural Stem Cells

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Twelve percent of pregnant women receive glucocorticoids (sGCs) to reduce the risks to reduce morbidity and mortality associated with preterm birth in infants. The two most commonly administered sGC are Dexamethasone (Dex) and Betamethasone (Beta) and they serve to decrease the severity of respiratory distress, intraventricular hemorrhage and necrotizing enterocolitis. However, repeated administration of sGC has been shown to be associated with adverse neurological outcome and depends on the type of sGCs used, dose, timing of sGCs administration and sex. We have previously shown that prenatal exposure to Dex in a murine model lead to sex specific changes in the transcription response and in the biological function of neural stem cells and to long-term changes in brain architecture and behavior. Beta is the predominant sGC used prenatally in the United States, therefore these studies investigated the cellular and molecular responses to beta exposure on the neural stem cells in-vitro and anatomical organization of the brain in-vivo. Murine NSCs were isolated from the E14.5 cerebral cortex and exposed to 10^{-7} M Dex, 10^{-7} M Beta, or Vehicle for 4 or 24 hours and the immediate and long-term impact on transcription, proliferation and neuronal, glial and oligodendrocyte differentiation examined. Affymetrix genome transcriptional analyses reveal sex specific responses to Dex vs Beta in 4 hours. In females 682 genes were differentially regulated by Dex compared to 576 by Beta. In contrast, 875 were altered by Dex and 576 by Beta in males (Fold change > +/- 1.5, P< 0.05). Select target genes were independently validated by QPCR. Ingenuity Pathway Analysis was used to identify unique and overlapping pathways that were altered by Dex vs Beta. In males, Dex uniquely altered 34 pathways including, Thyroid Hormone Metabolism, ERK5 Signaling and Opioid Signaling while Bata altered 33 pathways including, Phagasome formation, IL-7 Signaling and JAK STAT signaling. In Females, Dex altered 45 pathways including Calcium Signaling, Serotonin Receptor Signaling and Xenobiotic Signaling, while Beta altered 46 pathways including, FXR/RXR Activation, Tec Kinase Signaling and D-myo-Inositol-5-Phosphate Metabolism. Another 35 pathways were altered by both Dex and Beta but they showed differences in genes activated or repressed. Dex and Beta, both significantly altered genes involved in proliferation and differentiation therefore the biological response of NSC to sGCs stimulation in vitro and the long term consequences of sGC exposure in-vivo was compared. Distinct differences in cell proliferation, glial and oligodendrocyte differentiation were observed. These results reveal gene targets, cellular pathways and processes that are differentially altered by prenatal Dex vs Beta exposure. Our finds may provide insights into the sex specific neurological outcomes observed in children exposed to sGCs in-utero.

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A Novel Role of Nuclear and Membrane Receptor on Isoflavone-Induced Neuritogenesis and Synaptogenesis

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Thyroid hormone (TH) receptor (TR) and estrogen receptor (ER) play crucial roles in brain development. TR and ER are involved in dendrite growth, spines, and synapse formation in neurons. Soybean isoflavones, such as genistein, daidzein, and daidzein metabolite, S-equol are known to exert their action through TR, ER, and GPER1, a G-protein-coupled ER. However, the mechanisms of isoflavones action on brain development, especially during neuritogenesis and synaptogenesis, have not yet been extensively studied. We evaluated the effects of isoflavones using mouse primary cerebellar culture, astrocyte-enriched culture, Neuro-2A clonal cells, and co-culture with neurons and astrocytes. Soybean isoflavone augmented TH- or estradiol (E2)-mediated dendrite arborization of Purkinje cells. Such augmentation was suppressed by G15, a selective GPER1 antagonist, and ICI 182.780, an antagonist for ERs in both cultures. The knockdown of nuclear TRs or ERs also significantly reduced the dendrite arborization of Purkinje cells. It also increased the mRNA levels of TH-responsive genes, including *Mbp, Bdnf, Rc3, Ntf3*, *Camk2b, Hr*, and also *Syn1, Syp,* and *Psd95* that are involved in synaptic plasticity. Isoflavones also increased the protein levels of synapsin-1, synaptophysin, and PSD95 in dendrite and membrane fraction of the cerebellar culture. To study further the molecular mechanism, we used Neuro-2A clonal cells. Isoflavones also induced neurite growth of Neuro-2A. The knockdown of TRs, ERs, and GPR30 by RNAi reduced isoflavones-induced neurite growth. Moreover, the co-culture study of Neuro-2A and astrocytes also showed an increase in isoflavones-induces neurite growth. In addition, isoflavones increased the localization of synapsin-1 or synaptophysin and F-actin in filopodia tips during Neuro-2A differentiation. The knockdown of nuclear ERs or GPR30 significantly reduced the number of filopodia and synapsin-1 or synaptophysin expression levels in neurite and membrane fractions. However, there are no significant effects of

filopodia formation after co-culture with astrocytes. These results indicate that nuclear ERs and TRs play an essential role in isoflavones-induces neuritogenesis. Non-genomics signaling through membrane receptor and F-actin are necessary for the isoflavones-induces synaptogenesis. Astrocytes-neurons communication also increased isoflavones-induced neuritogenesis, but not synaptogenesis.

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

A Steroid Receptor Coactivator Stimulator MCB-613 Attenuates Adverse Remodeling After Myocardial Infarction

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Previous work from ours and other laboratories have shown that steroid receptor coactivators (SRCs) are involved in heart development and in mitigating cardiac dysfunction in cardiac injury models. Members of the p160 SRC family, SRC-1 (NCOA1), SRC-2 (NCOA2/TIF2/GRIP1) and SRC-3 (NCOA3/AIB1/ACTR/pCIP), interact with nuclear receptors and other transcription factors to drive target gene expression by assembling transcriptional coactivator complexes to increase transcription. This indicates a potential for SRC targeting drugs pertinent to cell migration, proliferation and survival-promoting paracrine interactions in cardiac tissue injury responses. We have identified a small molecule activator of SRCs (MCB-613) that selectively and reversibly binds to SRCs as shown by surface plasmon resonance and is a potent SRC stimulator that acts to greatly enhance SRC transcriptional activity with no apparent toxicity in mice. We postulated that MCB-613 could enable wound repair and preservation of cardiac function after an acute MI by reducing the extent of injury-related fibrosis and the subsequent chronic loss of cardiac function associated with non-contracting scar tissue. We thus tested the effect of MCB-613 on the cardiac injury response by administering MCB-613 two hours after ischemic injury in a mouse model of MI. Along with measurements of functional cardiac output and damage, we sought to identify the cell-type specific responses responsible for MCB-613's cardio-protective effects by utilizing single cell transcriptomics of cardiac interstitial cells to characterize the effects of SRC stimulation on cardiac function post-MI. We show that MCB-613, a potent small molecule stimulator of steroid receptor coactivators (SRCs) attenuates pathological remodeling post-MI. MCB-613 decreases infarct size, apoptosis, hypertrophy, and fibrosis while maintaining significant cardiac function. MCB-613, when given within hours post-MI, induces lasting protection from adverse remodeling concomitant with: (i) inhibition of macrophage inflammatory signaling and IL-1 signaling which attenuates the acute inflammatory response, (ii) attenuation of fibroblast differentiation, and (iii) promotion of Tsc22d3 expressing macrophages - all of which may limit inflammatory damage. Our results indicate MCB-613 controls the cellular interstitial cardiac repair response to ischemia. Distinct molecular and cellular mechanisms related to stimulation of SRC-3 have been identified that pave the way for the further exploration of SRCs as drug targets that can be engaged to improve the management of myocardial injury response outcomes. SRC stimulation with MCB-613 (and derivatives) is a potential novel therapeutic approach for inhibiting cardiac dysfunction after MI.

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

Androgen Receptor Blocker Improves the Cardiometabolic Profile in a Rat Model of Polycystic Ovary Syndrome, but at What Cost?

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Introduction: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. PCOS is characterized by androgen excess and ovulatory dysfunction high prevalence of cardiovascular risk factors such as increased blood pressure (BP), insulin resistance (IR), and obesity. We have demonstrated previously that exposing prepubertal female rats to dihydrotestosterone (DHT) leads to increase in food intake (FI), body weight (BW), BP, and IR. We tested the hypothesis that administration of the AR blocker bicalutamide (BICA) would decrease BP, IR, and obesity in PCOS model. As there are previous reports of severe hepatotoxicity with the AR blocker flutamide, we also examined BICA effects in the liver. **Methods:** Four-week old female Sprague Dawley rats implanted with DHT pellets (7.5mg/90 days) or placebo (PBO) were randomized to standard chow diet with or without the AR blocker bicalutamide (BICA) at a dose of 250 mg/kg/day throughout the study (n=10/group). BW and FI were measured weekly. BP and heart rate (HR) were measured by radiotelemetry. Fasting plasma was collected for IR (Homeostatic model assessment for IR, HOMA-IR). At euthanasia, the liver was collected, as well as plasma for gamma glutamyl transferase (GGT), alanine transaminase (ALT), and aspartate transaminase (AST) quantification. **Results:** PCOS rats had increased BW, FI, IR, and BP compared to PBO. BICA treatment had no impact on BW (285.3 ± 7.0 vs 270 ± 8.2 g, P=0.2) as well as FI and HR in PCOS. However, in PCOS, BICA decreased HOMA-IR (5.10 ± 0.40 vs 3.33 ± 0.31, P<0.05) and BP (115.4 ± 0.7 vs 105.3 ± 0.2 mmHg, P<0.01). Compared to PBO, PCOS+BICA rats had similar IR (3.83 ± 0.28 vs 3.33 ± 0.31, P=0.7) and BP (107.4 ± 0.8 vs 105.3 ± 0.2 mmHg, P=0.9). In addition, the liver weight to tibia length ratio was drastically increased by BICA in PCOS (222.9 ± 9.5 vs 360.4 ± 16.9 mg/mm, P<0.0001) as well as GGT (0.88 ± 0.88 vs 11.67 ± 0.58 U/L, P<0.0001), though it decreased AST (60.2 ± 6.9 vs 42.4 ± 1.9 U/L, P<0.05) and had no impact