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