agonists, a supposed "silent" heterodimer partner for TRs. These data showed RXR agonists can affect TR signaling at least in pituitary cells. We extended these results to our sensitive and specific *in vivo* model for TH action, *Xenopus laevis* metamorphosis. We previously demonstrated that RXR agonists like organotins and the pharmaceutical bexarotene, strongly potentiate (and RXR antagonists inhibit) TH induced metamorphic programs, at the morphological, cellular (e.g. apoptosis or proliferation), transgenic reporter gene levels, and transcriptomic responses in tadpole tails. We have now extended this analysis to include RNA-Seq experiments over distinct time points in the tadpole brain, a common target of TH in humans and frogs, revealing specific gene sets particularly affected by TH and RXR ligands working in concert. Very few genes were affected by RXR ligands alone. The remarkable overlap between the environmental toxicant tributyltin and the synthetic and specific RXR ligand bexarotene regulated transcriptomes provides strong evidence that they have a common molecular target in multiple tissues. We have also created germline mutations in all RXR family members in *Xenopus tropicalis* (alpha, beta and gamma), and both copies of the duplicated TR beta gene in *Xenopus laevis* via genome editing approaches. This will allow us to further investigate TR-RXR heterodimer function across tissues and developmental timeframes, and in response to known and suspected TR and RXR ligands. Our studies revealed an unanticipated degree of TR and RXR ligand interactions *in vitro* and *in vivo*, highlighting a surprising role of RXRs as avenues for TH endocrine disruption, including the brain.

Endocrine Disruption

ENDOCRINE DISRUPTING COMPOUNDS: MECHANISMS OF ACTION AND CLINICAL IMPLICATIONS

Developmental Programming: Prenatal Bisphenol A Induces Non-Monotonic Changes in Epigenetic Modulators in Metabolic Tissues of Female Sheep

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Developmental exposure to endocrine disruptor bisphenol A (BPA) is associated \with metabolic defects during adulthood in the female sheep. These are characterized by peripheral insulin resistance and increase in negative mediators of insulin sensitivity such as oxidative stress in metabolic tissues, lipotoxicity in liver and muscle and adipocyte hypertrophy in visceral (VAT) and subcutaneous (SAT) adipose tissue. Conceivably, developmental impact of BPA on regulators of insulin sensitivity involves changes in epigenetic machinery and mediated via changes in expression of enzymes that induce covalent modifications of DNA and histone. To determine the impact of prenatal BPA exposure on epigenetic enzymes [DNA methyltransferases (DNMT), histone deacetylases (HDAC), histone acetyl transferase EP300, histone methylases (SUV39H1, SMYD3 and EZH2) and histone demethylase KDM1A], metabolic tissues (liver, muscle, VAT and SAT) were collected from 21-month-old female offspring born to mothers treated with 0, 0.05, 0.5, or 5 mg/kg/day of BPA from days 30-90 of gestation. Data were analyzed by Cohen's effect size analysis and large magnitude differences (Cohens d>0.8) discussed. In liver, prenatal BPA induced: 1) a decrease in *DNMT1* and *3B* at all doses and *DNMT3A* at the highest dose, 2) a decrease in histone deacetylase *HDAC3* as opposed to increase in acetylase *EP300* at the highest dose, 3) a decrease in *SUV39H1* at the two higher doses, and 4) an increase in *EZH2* only with 0.5 mg dose. The prenatal BPA-induced changes in muscle include: 1) increases in expression of DNMTs and *EP300* at all doses, 2) an increase in *SUV39H1* at 0.5 mg dose and *EZH2* at 0.05 and 0.5 mg doses, and 3) decreases in *SMYD3* at the lowest dose and *KDM1A* with 0.05 and 5 mg doses. Prenatal BPA treatment also induced depot-specific changes at the adipose tissue level. In the VAT prenatal BPA induced: 1) increases in expression of all DNMTs examined 2) increases in *HDAC2* at all doses except *HDAC3* only at 0.05 and 0.5mg dose and 3) increases in histone acetylase *EP300* at all doses. In SAT BPA induced: 1) decrease in *DNMT3A* at 0.5mg and increase at 5 mg, 2) decreases in *HDAC1* and *HDAC2* at the lowest dose, 3) an increase in *HDAC3* at the medium dose, and 4) a decrease in *EP300* at the lowest dose. Contrasting changes in histone methylation modifying enzymes were also evident between VAT and SAT manifested as increases in *SUV39H1* at the two higher doses and *SMYD3* at all three doses in the VAT as opposed to decrease in *SUV39H1* and *SMYD3* at 0.05 and 0.5 mg doses and *EZH2* and *KDM1A* at the lowest dose in the SAT. These findings indicating developmental exposure to BPA induces non-monotonic dose responses in epigenetic modifying enzymes are consistent with the premise that changes in epigenetic machinery underlie the metabolic disruptions induced by prenatal BPA treatment likely accounting for the tissue specific changes in insulin sensitivity. (support by R01-ES-016541)

Endocrine Disruption

ENDOCRINE DISRUPTING COMPOUNDS: MECHANISMS OF ACTION AND CLINICAL IMPLICATIONS

Effects of Gestational Bisphenol A Exposure on Hypothalamic Vasopressinergic Neurons

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Background: Bisphenol A (BPA), a well-recognized endocrine disruptor that has been linked to numerous adverse outcomes, is ubiquitously detected in humans, including pregnant women. Emerging epidemiological and animal studies showed associations between prenatal BPA exposure and social-behavioral issues in childhood, including aggression and anxiety.
Methods: Since vasopressinergic circuits play important roles in regulating social behaviors, and our previous studies showed that prenatal exposure to BPA altered vasopressin development in offspring, here we evaluated effects of BPA on the number of arginine vasopressin (AVP) neurons in hypothalamic subregions, including the supraoptic nucleus (SON), suprachiasmatic nucleus (SCN) and paraventricular nucleus (PVN), using immunohistochemistry,