

to show that treatment with 10 β ,17 β -dihydroxyestra-1,4-dien-3-one (DHED, a brain-selective bioprecursor prodrug of 17 β -estradiol (E2) will ease ADT-associated hot flushes without feminizing side-effects.

To evaluate the effect of DHED on hot flushes the pharmacological rat hot flush model was used. Orchiectomized (ORDX) rats were treated orally with three different doses (10, 30, and 100 μ g/kg) of DHED or ethynyl estradiol (EE, 200 μ g/kg) for ten days. They were addicted to morphine and the tail skin temperature (TST) of saline-treated rats raised by 4.4 \pm 0.5 $^{\circ}$ C when morphine effect was withdrawn with naloxone injection. DHED and EE treatments significantly lowered such TST rise from 4.4 $^{\circ}$ C to 2.9 \pm 0.5 $^{\circ}$ C and 1.8 \pm 0.5 $^{\circ}$ C, respectively.

The conversion of DHED to E2 in the brain was confirmed by measuring the effect of DHED-derived E2 on the expression of progesterone receptors (PR) in the preoptic area of the hypothalamus with *in situ* hybridization histochemistry. Both DHED and EE treatment stimulated PR expression compared to saline-treatment in ORDX rats.

In our previous studies, we have shown the lack of conversion of DHED to E2 in the periphery in ovariectomized female rats; i.e., DHED treatment did not have uterotrophic, mammatrophic activities and did not stimulate galanin expression in the anterior pituitary. In these studies, the lack of conversion of DHED to E2 was also confirmed in male rats by measuring the expression of galanin, a highly estrogen-regulated gene, in the pituitary with quantitative RT-PCR. Contrary to EE, DHED treatment did not stimulate galanin expression in this estrogen target.

These observations support subsequent translational research focusing on DHED's therapeutic use to remedy hot flushes and potentially other neurological symptoms in prostate cancer patients undergoing ADT to manage their malignancy. An estrogen therapy with the brain-selective DHED would provide a safe approach to prevent these neurological symptoms without causing peripheral estrogenic side effects such as gynecomastia or deep vein thrombosis.

Diabetes Mellitus and Glucose Metabolism

ISLETS, LIVERS, PLACENTA, AND VASCULATURE — THE MULTITISSUE IMPACT OF DIABETES

FSTL3 Neutralizing Antibodies Restore Function to Diabetic Mouse and Human Islets: A New Approach for Treating Diabetes

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Activin, GDF11 and myostatin are structurally related members of the TGFbeta superfamily of growth factors with many biological roles in animal models and humans. Their actions are neutralized by extracellular proteins such as follistatin and follistatin like-3 (FSTL3). We have previously demonstrated that genetic inactivation of *Fstl3* results in enlarged pancreatic islets containing increased

numbers of beta cells that produce more insulin in response to glucose compared to wild type litter mates. We further discovered that at least some of these new beta cells arise via transdifferentiation from alpha cells. We also demonstrated that functional human islets from normal donors produce very high levels of activin. In contrast, activin biosynthesis is vastly reduced and FSTL3 synthesis is significantly increased in human islets from diabetic donors suggesting that activin is critical for normal insulin production. This was substantiated by direct treatment of human diabetic islets with activin which restored their response to glucose. These observations support the hypothesis that an FSTL3 neutralizing antibody would constitute a novel therapeutic approach to curing diabetes through restoring beta cell function as well as accelerating generation of new beta cells through transdifferentiation. To test this hypothesis, we produced a mouse monoclonal antibody that neutralized hFSTL3 (FP-101), thereby releasing bioactive activin, GDF11, and myostatin. We have now tested this antibody for biological activity *in vitro* on mouse and human islets. We used islets from high fat diet (HFD) treated *mice* to model diabetes-inducing effects of obesity as well as 24-hour incubation in hyperglycemic (33 mM glucose) medium to create *human* islets that lose responsiveness to high glucose as a model for human diabetes. In mouse islets we found that stimulation of normal (chow diet) islets by high glucose produced a stimulation index (SI) of 3.5 that was reduced to 2 in HFD islets. Treatment with activin, FP-101, or a commercial polyclonal antibody to mFSTL3 all increased response of HFD islets to elevated glucose and partially restored SI to normal levels. In human islets, hyperglycemia eliminated the normal (2.5 SI) response to high glucose while activin or FP-101 treatments dose-responsively restored this response. These results demonstrate that anti-FSTL3 therapy can restore function to compromised beta cells from mouse and human diabetes models. The observation that activin has the same action as anti-FSTL3 antibody indicates that FP-101 works through enhancing the activin signaling pathway. Finally, these results demonstrate that the FSTL3-activin pathway is an important regulator of beta cell function in humans as well as mice, supporting further development of this therapy as a diabetes treatment.

Genetics and Development (including Gene Regulation)

ENDOCRINE DISRUPTING CHEMICALS

Region-Specific Effects of the Exposome on Brain Monoamine Levels in Female Rats

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Prenatal programming with endocrine disrupting chemicals (EDCs), in particular the ubiquitous plasticizers

bisphenol A (BPA) and di(2-ethylhexyl) phthalate (DEHP), can induce long-lasting behavioral changes in rats. Additionally, changes in estrogen are correlated with the development of mood disorders in women; however, the underlying neurobiological mechanisms are unclear. This study was conducted to determine the cumulative effects of prenatal exposure to EDCs followed by chronic estradiol treatment in adult female rats on monoamine levels in the prefrontal cortex (PFC) and hippocampus (HC). Dams were orally administered saline (control; 10 μ L/kg), BPA (B; 5 μ g/kg), DEHP (D; 7.5 mg/kg) or a combination of BPA+DEHP (B+D) during days 6 through 21 of pregnancy. Adult female offspring were sham-implanted or implanted with pellets that release 17 β -estradiol (E2) for 90 days (20 ng/day; Innovative Research America). The offspring then underwent a battery of behavioral tests at the end of treatment. Brains collected from the offspring were sectioned and the PFC and HC were microdissected and analyzed for levels of norepinephrine (NE), dopamine (DA) and serotonin (5-HT), using High-Performance Liquid Chromatography (HPLC). Significant reductions in monoamine levels were observed in the PFC while NE and 5-HT levels were markedly reduced in the HC after prenatal exposure to D or BD. BPA's effects on monoamines were comparatively modest. E2 exposure increased DA but decreased 5-HT levels in the PFC of control animals. Prenatal exposure to EDCs made the offspring non-responsive to E2. The marked reduction in monoamine levels could have implications for learning and memory.

Genetics and Development (including Gene Regulation)

ENDOCRINE DISRUPTING CHEMICALS

Prenatal Exposure to Bisphenol A, S and F Increases Blood Pressure in Female Rats

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Cardiovascular diseases are the leading causes of mortality among men and women. With the new blood pressure guidelines from the American Heart Association, almost half of the United States population has hypertension (45.6%). The reasons for this high prevalence of hypertension in our population could be several, but the effect of emerging contaminants are overlooked and understudied. Bisphenol-A (BPA) is a widely used plasticizing agent that contaminates the environment. Most humans are exposed to BPA on a daily basis and urine levels of this endocrine disrupting chemical (EDC) are positively correlated with hypertension. The FDA banned the use of BPA in baby bottles in 2012, however, it is still being used in food containers and plastics. Currently, several BPA analogs such as bisphenol-S (BPS) and bisphenol-F (BPF) are used to replace BPA in the plastic industry. But their physiological effects are not clear. In order to study the effects

of these EDCs on the development of hypertension, we exposed pregnant Sprague Dawley (SD) rats to saline, 5 μ g/Kg BW of BPA, BPS or 1 μ g/kg BW of BPF. The offspring were allowed to reach adulthood before implantation with a radiotelemeter (Data Sciences International; HD-S10) in the femoral artery for undisturbed monitoring of systolic, diastolic and mean arterial blood pressure and heart rate. Recordings were measured once a week for 11 weeks over 24 hours to establish day and night readings. Night-time systolic BP was significantly elevated in BPA, BPF and BPS exposed rats compared to control. During the day, systolic BP was significantly higher in the BPA group compared to control. Diastolic BP was elevated in the BPS and BPF groups. Heart rate was elevated the most in the BPS group. These results indicate that prenatal exposure to low levels of BPA analogs has a profound effect on hypertension.

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS I

Familial Paranglioma Syndrome: A Rare Case of Secondary Hypertension in Young People

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FAMILIAL PARAGANGLIOMA SYNDROME: A RARE CASE OF SECONDARY HYPERTENSION IN YOUNG PEOPLE

Parangliomas are rare tumors originating in the autonomic nervous system, whose clinical manifestations are the result of excessive production of catecholamines.

We present a case of a 26-year-old female with 5 years of disease characterized by episodic profuse sweating, headaches and high blood pressure refractory to antihypertensive treatment. She also had intermittent palpitations which intensified 1 month before admission. Patient was cataloged with diagnosis of endocrine hypertension. She had elevated urinary fractionated metanephrines, elevated plasma normetanephrin and plasma chromogranin A (CgA). Subsequently, an abdominal CT study was performed, finding a solid ovarian mass of defined edges located in retroperitoneal space, an intercave region immediately preceding the L2-L3 intervertebral disc that measured 26.2 x 23.9 x 28.8 mm. It was also found bilateral tumours at cervical level of 14 mm in right side and 10 mm in left side, suggestive of paranglioma by magnetic resonance imaging (MRI).

With a suspected diagnosis of paranglioma of Zuckerkandl's organ, beta and alpha-adrenergic blockage were carried out and surgical intervention was done by a block resection of the tumour. Anatomopathological diagnosis confirmed the suspicion of well-delimited capsulated paranglioma of 2.0 X 1.0 X 0.3 cm, with low mitotic index (<2) and a result of positive sinaptophysin by immunohistochemistry. She reached complete remission and normal determinations in urine of catecholamines and methanephrines. Currently the patient is in follow-up with favorable evolution and succinate dehydrogenase type B (SDHB) gene test is pending.

Despite infrequency of parangliomas, it is important to take them into account in the differential diagnosis of