Online Proceedings

SESSION 1D

MEDICAL THERAPEUTICS AND ENDOCRINOLOGY

Session Moderator: Ian Sweet, Medicine
231 MGH
1:15 PM to 2:45 PM
* Note: Titles in order of presentation.

Maternal Low Protein Diet Alters Clearance of Uric Acid and Creatinine in Rat Offspring
Tahir Mahmood, Senior, Biochemistry
Mentor: Ganesh Cherala, Pharmacy Practice, Oregon State University
Mentor: Barent DuBois, College of Pharmacy, Pharmacy Practice, Oregon State University
Mentor: Jacob Pearson

Abnormal perinatal environment, commonly manifested as low birth weight, has been associated with birth defects as well as chronic disease. In particular, studies have shown low birth weight to have a deleterious association with type II diabetes, hyperlipidemia, hypertension, cardiovascular disease, renal disease, and renal failure. Of specific interest are the mechanistic details concerning low birth weight subjects' altered excretion. Maternal low protein diet (LPD) during gestation and lactation results in offspring with significantly lower birth weight. Using the maternal LPD rat model, we determined renal excretion of select endogenous compounds by collecting blood and urine at various times of age. Clearance of creatinine and uric acid are indicators of glomerular filtration rate and reabsorption, respectively. High Performance Liquid Chromatography assays were used to simultaneously quantify creatinine and uric acid in the urine and in the blood of the rat. It was found that creatinine clearance and uric acid clearance decreased in LPD rats in an age-dependent and sex-specific fashion. Specifically, there were observed significant decreases in both creatinine clearance and uric acid clearance in LPD male offspring at both age's day 90 and day 120 old. No differences were observed in both creatinine clearance and uric acid clearance in LPD female offspring until age day 120 old indicating an age-dependent programming of females as opposed to males. The results strongly correlate with decreased and altered excretion observed in low birth weight subjects and suggest that perinatal LPD has a long-term programming of renal excretion. These findings could partially explicate the underlying mechanisms that lead to higher incidence of renal disease/dysfunction in perinatally growth restricted subjects. Furthermore, altered renal function could affect the renal handling of therapeutic agents and thus affecting the overall treatment outcomes in low birth weight subjects.

POSTER SESSION 3

Balcony, Easel 121
2:30 PM to 4:00 PM

Diabetes, Obesity, and Ossabaw Pigs
Kristin Nancy Kontogianis, Senior, Biochemistry, Business Administration (Human Resources Management)
Mary Gates Scholar
Mentor: David Flum, Surgery
Mentor: Yuki Aoki, Surgery

Obesity is a growing epidemic. Consequently, the percentage of Americans living with Type 2 Diabetes Mellitus (T2DM) has increased; 25.8 million Americans suffer from diabetes, and 90-95% of adult diabetes is T2DM. Bariatric surgeries–gastrointestinal operations designed to encourage weight loss by rerouting and reconnecting various parts of the stomach and small intestine–have been developed in response to increased obesity. A ramification of these surgeries is the elimination of T2DM; 84% of patients with T2DM experienced complete remission of diabetes after bariatric surgery. At RYGB Mechanisms (RYGBM) Animal Lab, we seek to understand the mechanisms of weight loss and T2DM remission in bariatric surgery through the development of an animal model. The animal models selected for this research are Ossabaw pigs. These pigs, raised on high fat diets, are obese and naturally develop insulin intolerance similar to T2DM in humans. There are two leading hypotheses for the causal relationship of bariatric surgery and the elimination of T2DM: the Lower Intestinal Hypothesis and the Upper Intestinal Hypothesis. To test these hypotheses, we perform five variations of bariatric surgery on the animal models: Gastrojejunostomy (GJ), GJ with Duodenal Exclusion, Roux-En-Y Gastric Bypass (RYGB), RYGB with Vagotomy, and Sham operation. We perform these variations of surgeries in attempts to identify which procedures will decrease T2DM while being the least invasive and most recoverable. Pre-operative and post-operative weights indicate if the surgery worked as a weight

loss mechanism, while the pre-operative and post-operative changes in insulin sensitivity and gut peptide hormones–ghrelin, PYY, GLP1–indicate if the procedure succeeded as a T2DM loss mechanism. Since the start of the study, survival rates have improved, and RYGBM compilation of data has increased, thus enhancing conclusive findings, though data to support either hypothesis is still in progress.

POSTER SESSION 4

MGH 241, Easel 157

4:15 PM to 5:45 PM

Characterization of Novel Chemical Inhibitors for the Plasma Membrane Monoamine Transporter and Organic Cation Transporter 3

Ji Soo Kim, Senior, Bioengineering, Biochemistry
Mentor: Joanne Wang, Pharmaceutics
Mentor: Haichuan Duan, Pharmaceutics

Deficiencies of monoamine neurotransmitters including serotonin, norepinephrine, and/or dopamine have been associated with many CNS diseases including depression, schizophrenia, ADHD, autism, Parkinson's disease, and Tourette syndrome. The intensity and duration of monoamine signaling is mainly determined by the clearance of the released transmitters through uptake1 and uptake2 transporters. The recently discovered uptake2 transporters including the plasma membrane monoamine transporter (PMAT) and organic cation tansporter3 (OCT3) have been less studied partly due to the lack of specific inhibitors. Recently, inhibition of PMAT and/or OCT3 has been proposed as a strategy for the development of antidepressant drugs with improved efficacy and faster onset of actions. The goal of this project is to characterize specific chemical inhibitors for PMAT and OCT3. Previously, 10-40 small molecule inhibitors for PMAT and OCT3 were identified from high throughput screening. We will choose two to three inhibitors for PMAT and OCT3 obtained from the initial screen and further analyze their potency, specificity and mechanism of inhibition towards PMAT and OCT3. We first will determine their inhibition potencies (IC50) towards PMAT and OCT3 using radiotracer uptake assays in cell lines stably expressing these transporters. Preliminary data showed that two compounds inhibited OCT3 with IC50 values of 1.97 ± 0.766 and 2.86 ± 0.532 μM. One compound inhibited PMAT with an IC50 value of 2.15 ± 0.537 μM. Further studies will be performed to determine the specificity and mechanism of inhibition for these inhibitors. The proposed studies may lead to novel, highly specific and potent PMAT and OCT3 inhibitors that could be further evaluated and developed in preclinical models for the treatment of depression and other monoamine-related diseases.