SUN-255

17-alpha-hydroxyprogesterone caproate (17-OHPC) is a synthetic progestin commonly prescribed for the prevention of recurrent preterm birth. Treatment with 17-OHPC in high-risk pregnant women begins between gestational weeks 16-20, and continues through week 36 [1]. Recent studies suggest that 17-OHPC is not an effective treatment for reducing rates of preterm delivery [2,3]. Most concerning is the timing of 17-OHPC administration, which coincides with critical periods of mesocortical dopamine pathway development in the fetus [4]. Regulating behaviors of executive function, the mesocortical pathway originates in dopaminergic neurons of the ventral tegmental area (VTA) that innervate the medial prefrontal cortex (mPFC). Disruptions in mesocortical dopamine pathway development are believed to underlie deficits in cognitive functioning [5,6].

In rodent models of cortical development, the developing mesocortical dopamine pathway is sensitive to progestins. There is transient expression of nuclear progesterone receptors (PR) in both the VTA and mPFC [7]. PR are powerful transcription factors that can alter gene expression and fundamentally alter neural development [8,9]. When rodents are treated with 17-OHPC during mesocortical dopamine pathway development, there are significant sex-specific alterations in dopaminergic innervation of the mPFC and deficits in cognitive behaviors in adulthood [10]. Microglia, the resident immune cells of the central nervous system, play a critical role in establishing dopaminergic circuitry of the forebrain [11]. The following experiment tested the hypothesis that 17-OHPC alters microglia activity in a sex-specific manner.Our results reveal that there is an innate sex difference in the number of reactive microglia, where control group

females had significantly more than males. Treatment with 17-OHPC abolishes this sex difference by reducing the number of reactive microglia in 17-OHPC treated females to male-like levels in both the prelimbic (PL) and infralimbic (IL) mPFC. There is also a significant reduction in the percentage of reactive microglia in 17-OHPC treated animals compared to controls. These results suggest that early 17-OHPC exposure may decrease functional microglial activity during critical periods of cortical development, and that females are more vulnerable than males. Consideration should be given to the potential effects of 17-OHPC on neural and cognitive development in children.

Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

Next Generation AR Antagonists Increase Systemic Active Glucocorticoid Exposure by Altering Glucocorticoid Metabolism

Mohammad Alyamani, PhD[1], Nima Sharifi, MD[1], Jianbo Li, PhD[1], Mona Patel, MS[1], Michael Berk, MS[1], Susan Taylor, BSN[1], Christopher Przybycin, MD[1], Edwin M. Posadas, MD[2], Ravi Madan, MD[3], James L. Gulley, MD, PhD, FACP[3], Brian I. Rini, MD, FACP[1], Jorgi A. Garcia, FACP, MD[1], Eric A. Klein, MD[1].

[1]Cleveland Clinic, Cleveland, OH, USA, [2]Cedars-Sinai Medical Center, Los Angeles, CA, USA, [3]The National Cancer Institute at the National Institutes of Health, Bethesda, MD, USA.

SUN-739

Enzalutamide and apalutamide are potent next-generation androgen receptor (AR) antagonists used in metastatic and non-metastatic prostate cancer. Despite the increased survival benefits of these agents, resistance normally occurs and the disease transitions to its lethal form. We hypothesized that enzalutamide and apalutamide suppress 11β-hydroxysteroid dehydrogenase-2 (11β-HSD2), which normally converts cortisol to cortisone, leading to elevated cortisol concentrations and increased ratio of active to inactive glucocorticoids. We measured cortisol and cortisol/cortisone ratio (substrate/product of 11β-HSD2) in serum using mass spectrometry before and 1 month on-treatment in 3 clinical trials: 1) neoadjuvant apalutamide + leuprolide (n=25) 2) enzalutamide +/- PROSTVAC for metastatic castration-resistant prostate cancer (n=54) and 3) enzalutamide +/- PROSTVAC for non-metastatic castration-sensitive prostate cancer (n=38 patients). Progression-free survival (PFS) was determined in the metastatic CRPC study of enzalutamide +/- PROSTVAC for those with glucocorticoid changes above and below the median. A statistically significant rise in cortisol concentration and cortisol/cortisone ratio with AR antagonist treatment occurred uniformly across all 3 clinical trials. For example, a rise in cortisol/cortisone ratio occurred in 23/25 (92%) patients ($p < 0.001$), 36/54 (67%) patients ($p < 0.001$), and 30/38 (79%) patients ($p = 0.051$), in the 3 respective trials. In the trial of enzalutamide +/- PROSTVAC for metastatic CRPC, high cortisol/cortisone ratio in the enzalutamide arm was associated with significantly improved PSA progression-free survival and radiographic progression-free survival. However, in the enzalutamide + PROSTVAC arm, the opposite trend was observed. In conclusion, treatment with enzalutamide or apalutamide increases systemic exposure to active glucocorticoids. These findings have potential consequences for immune suppression and the efficacy of treatment combinations using next-generation AR antagonists. On-treatment, glucocorticoid changes might serve as a pharmacodynamic biomarker.

Diabetes Mellitus and Glucose Metabolism

CLINICAL AND TRANSLATIONAL STUDIES IN DIABETES

Prandial Insulin Dosing Based on Carbohydrate Content Does Not Significantly Improve Glycemic Control in Hospitalized Patients with Diabetes

HEENAM GOEL, MBBS[1], Farheen K. Dojki, MD[2], Dawn Belt Davis, MD,PHD[3].

[1]UNIVERSITY OF WISCONSIN, Madison, WI, USA, [2]University of Illinois at Chicago, Chicago, IL, USA, [3]University of Wisconsin - Madison, Madison, WI, USA.

MON-663

Introduction: Diabetes mellitus (DM) is a highly prevalent concern in hospital medicine. In-hospital hyperglycemia and hypoglycemia are common. Hospitalized patients have variable and unpredictable amounts of carbohydrate content in their meals. We hypothesized that order sets that allow for flexible dosing of prandial insulin using an insulin to carbohydrate ratio (ICR) would provide