Adrenal

ADRENAL - CORTISOL EXCESS AND DEFICIENCIES

Discovery and Identification of Late Stage Selective Nonpeptide ACTH Antagonists for the Treatment of Cushing's Disease, Ectopic ACTH Secreting Tumors, and Congenital Adrenal Hyperplasia

Ana Karin Kusnetzow, Ph.D., Sangdon Han, PhD, Melissa A. Fowler, PhD, Jon Athanacio, MS, Greg Reinhart, BS, Elizabeth Rico, Ph.D., Sun Hee Kim, PhD, Michael Johns, BS, Taylor A. Kredel, BS, Agnes Antwan, BS, Oleg Tsivkovski, BS, Julie Nguyen, BS, Christine Staley, BS, Hannah Tan, BS, Rosa Luo, PhD, Stacy Markison, Ph.D., Ajay Madan, Ph.D., Yun Fei Zhu, PhD, Scott Struthers, PHD, Stephen F. Betz, PHD.
Crinetics Pharmaceuticals, San Diego, CA, USA.

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Adrenocorticotropic hormone (ACTH) is an important modulator of steroidal hormone synthesis and secretion from the adrenal gland and its selective activity at the melanocortin type 2 receptor (MC2) dictates the synthesis and secretion of cortisol (corticosterone in rats). Excess ACTH action contribute to the pathophysiology of Cushing's disease (CD), ectopic ACTH secreting tumors (EAS), and Congenital Adrenal Hyperplasia (CAH). Cushing's disease results from a microadenoma derived from pituitary corticotrophic cells that secretes excess ACTH, whereas EAS arises from nonpituitary ACTH secreting tumors. Excess ACTH action at the adrenal gland and resulting hypercortisolemia presents in a myriad of symptoms that result in high morbidity. CAH results from inactivating mutations in steroid synthesis pathways, resulting in lack of cortisol and aldosterone production. Lack of negative feedback by cortisol at the level of the pituitary causes the over-secretion of ACTH, and overproduction of adrenal androgens, causing significant virilization and reduction in quality of life. We hypothesize that blocking ACTH action directly via a selective MC2 receptor antagonist may provide an important new therapeutic mechanism for these patients.

To test this hypothesis, Crinetics launched an iterative medicinal chemistry program to identify potent and selective nonpeptide ACTH antagonists with pharmaceutical and safety characteristics suitable for evaluation in human clinical trials. Unlike most other G protein coupled receptors, MC2 requires the presence of an accessory protein (MRAP) for cell surface expression and recognition of ACTH. Using CHO-K cells stably expressing this MC2-MRAP complex, iterative optimization led to the discovery of multiple chemical classes of highly potent, nonpeptide MC2 receptor selective antagonist leads, which were then further optimized for drug-like characteristics. We identified multiple compounds that exhibit high potency for human and rat MC2 receptors (hMC2 K_b <1 nM), while having no activity at the MC1, MC3, MC4, or MC5 receptors. Leading ACTH antagonists were also evaluated for drug like characteristics, including good stability in liver microsomes, lack of inhibition of cytochromes P450 and the hERG ion channel, and were shown to exhibit good exposure upon oral dosing in both rats and dogs. These ACTH antagonists acutely suppress corticosterone secretion in an ACTH-challenge model in rats. In a 7-day hypercortisolemia model in which rats receive an implanted minipump that continually secretes ACTH, corticosterone levels were decreased, and body weight loss and adrenal hypertrophy were prevented with ACTH antagonist treatment. The culmination of these studies has led to a subset of candidate molecules that are being evaluated in genotoxicity, safety pharmacology, and general toxicology studies to enable evaluation in human clinical trials.

Adipose Tissue, Appetite, and Obesity

RARE CAUSES AND CONDITIONS OF OBESITY: PRADER WILLI SYNDROME, LIPODYSTROPHY

Electronic Cigarette Exposure Induces Pro-Inflammatory Changes in Adipose Tissue in Apolipoprotein E (APOE) Knockout Mice

Jorge Espinoza-Derout, Ph.D, Xuesi M Shao, MD, Jocelyn Molina-Mancio, BS, Kamrul M Hasan, PhD., Norma Mtume, MS, Amiya P. Sinha-Hikim, MS,PHD, Theodore C. Friedman, MS,MD,PHD.
Charles R. Drew University of Medicine and Science, Los Angeles, CA, USA.

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Electronic nicotine delivery systems or electronic cigarettes (e-cigarettes) are becoming exceptionally popular in the world as an alternative to conventional nicotine cigarettes, both in smokers and people who have never smoked. Nicotine can induce lipolysis in adipose tissue, leading to increased serum free fatty acids (FFA). Increased levels of FFA are one of the key elements in inducing a pro-inflammatory response and lead to ectopic lipid accumulation, lipotoxicity, mitochondrial dysfunction and metabolic disease. Our laboratory has shown that chronic e-cigarette exposure induces cardiac dysfunction, atherosclerosis and hepatic steatosis in the ApoE knockout (KO) model associated with increased levels of serum FFA. In this study, we investigated the role of adipose tissue in the metabolic changes associated with e-cigarette exposure. ApoE KO mice were exposed to saline, e-cigarette without nicotine [e-cigarette (0%)] and e-cigarette with 2.4% nicotine [e-cigarette (2.4%)] aerosol for 12 weeks. Western blot analyses from adipose tissue showed that mice treated with e-cigarette (2.4%) had decrease levels of SIRT1 when compared to mice treated with saline or e-cigarette (0%). Transcriptomic analysis of the differentially expressed genes shows a differential transcriptional response to e-cigarette (2.4%) in adipose tissue in comparison with e-cigarette (0%) or saline. The RNA-seq examination using ingenuity pathway analysis (IPA) software, revealed dysregulation of fibrosis, agranulocyte and granulocyte adhesion and diapedesis pathways in e-cigarette (2.4%) -exposed adipose tissue. Overall, we found an inflammatory phenotype associated with decreased levels of SIRT1 in adipose tissue of mice treated with e-cigarette (2.4%). Understanding the consequences of e-cigarette use on metabolic disease is directly relevant to the development of policies related to e-cigarette use.

Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

RORγ Is a Master Regulator of Tumor Lipid Metabolism

Hong-Wu Chen, Ph.D.