Histone deacetylase inhibitors as novel therapeutics in cardiometabolic syndrome

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Background: The histone deacetylases (HDAC) play an important role in the transcriptional regulation of eukaryotic gene expression by modifying the acetylation state of histones and other important proteins. The HDAC enzymes are composed of 18 family members classified in four classes depending on sequence identity and domain organization. The 11 so-called classical HDAC enzymes of class I, II, and IV are Zn²⁺ dependent. The remaining seven class III HDAC enzymes are referred to as sirtuin (SIRT) enzymes and require NAD⁺ as an essential cofactor. Aberrant HDAC enzyme function has been implicated in many diseases including various forms of cancer, asthma and allergic diseases, and inflammatory and CNS disorders. Previously we showed evidence that inhibition of histone deacetylases (HDAC) attenuate development of hypertension in DOCA-induced hypertensive rats and spontaneously hypertensive rats.

Objective: We hypothesized that HDAC inhibition attenuates development of hypertension and hyperglycemia induced by Cushing’s syndrome.

Methods and Results: Expression of target genes was measured by quantitative real-time PCR (qPCR). Recruitment of hormone receptor on promoters of target genes was analyzed by chromatin immunoprecipitation (ChIP) assay. Interaction between hormone receptor and HDACs was analyzed by co-immunoprecipitation (CoIP). Animal model of Cushing’s syndrome was established by subcutaneous implantation of osmotic mini-pump containing dexamethasone (Dex, 10 µg/day) or adrenocorticotrophic hormone (ACTH, 40 ng/day) for 4 weeks. Blood pressure was determined by tail-cuff method. Blood glucose level was analyzed by Accu-Check Performa. Dex and ACTH infusion induced hypertension and hyperglycemia which were attenuated by administration of valproic acid (VPA), a class I and IIa HDAC inhibitor. Expression of hormone target genes related with sodium reabsorption and gluconeogenesis was elevated by Dex and ACTH infusion, which was repressed by VPA administration in the kidney. In addition, enrichment of hormone receptor and RNA polymerase II on the promoters of target genes was elevated by Dex and ACTH infusion, which was attenuated by VPA administration.

Conclusion: HDAC inhibition attenuates development of hypertension and hyperglycemia induced by Cushing’s syndrome.