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Posttranslational modification of mineralocorticoid receptor as a therapeutic target in hypertension

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The transcriptional activity of steroid receptors is mainly regulated by ligand, however, post-translational modifications (PTM), such as phosphorylation, acetylation, ubiquitylation, and sumoylation, also play an important role in their stabilization, nuclear translocation, or transcriptional activity.
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 for transcription. 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.
I will present evidence that inhibition of histone deacetylases (HDAC) attenuated development of hypertension in DOCA-induced hypertensive rats and spontaneously hypertensive rats. Treatment with a HDAC class I inhibitor resulted in reduced expression of MR target genes in accordance with reduced recruitment of MR and RNA polymerase II (Pol II) on promoters of target genes. HDACi promoted MR acetylation, leading to decreased transcriptional activity of MR. Knockdown or inhibition of HDAC3 resulted in reduced expression of MR target genes induced by mineralocorticoids. Treatment of SHR with VPA increased MR acetylation without affecting MR expression, which attenuated development of hypertension in SHR. Although VPA treatment increased histone 3 acetylation (H3Ac) and fourth lysine trimethylation (H3K4me3) on promoter regions of MR target genes, it decreased expression of the target genes as well as recruitments of MR and Pol II.
The results indicate that posttranslational acetylation of MR is its regulatory mechanism for modulation of transcription activity.