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Role of the histone deacetylases and angiotensinogen transcription in obesity-induced hypertension model.

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Objectives: Epigenetics provides a new approach a variety of diseases, including obesity and metabolic diseases. Among them, histone/non-histone protein acetylation and deacetylation plays an important role in the regulation of gene expression, and expression of angiotensinogen is involved in the development of hypertension. In the previous study, we revealed the effect of pan-histone deacetylase (HDAC) inhibitor valproic acid in high-fat diet (HFD)-induced angiotensinogen expression and hypertension. In this study, we investigated the effect and underlying mechanism of a specific HDAC1 and HDAC2 inhibitor FK228 in HFD-induced angiotensinogen transcription and hypertension in mice.

Methods: C57BL/6 mice were fed either normal diet (ND) or HFD. When a HFD group became hypertensive, FK228 was administered for 17 days into both ND and HFD group. Blood pressure (BP) was measured using a noninvasive tail-cuff system. Serum angiotensin II (Ang II) concentration was measured by Ang II enzyme immunoassay. Interaction and binding of HDAC with transcription factors was analysed by Co-immunoprecipitation, proximity ligation assay, and chromatin immunoprecipitation assay.

Results: HFD accelerated the increase in body weight, systolic BP and diastolic BP. HFD increased angiotensinogen expression in the kidneys as well as Ang II in the serum. FK228 administration lowered BP, decreased expression of angiotensinogen in kidney and serum Ang II concentration. Gene silencing of HDAC1 in HRPTEpi cells decreased the expression of angiotensinogen. HFD increased nuclear expression of HDAC1 and transcription factor c-Myc, and FK228 reversed it. Interaction of HDAC1 and c-Myc in the chromatin and promoter region of angiotensinogen gene was increased in HFD and FK228 reversed it. Proximity ligation assay confirmed the interaction of HDAC1 and c-Myc increased by HFD, and reversed by FK228.

Conclusions: FK228 ameliorated obesity-induced hypertension by decreasing the binding of HDAC1 and c-Myc at the promoter region of angiotensinogen. FK228 acts as a novel therapeutic option for obese hypertension.