HDAC6 inhibition improves diastolic function in a mouse model of heart failure with preserved ejection fraction

Authors

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Abstract

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Background: Heart failure with preserved ejection fraction (HFpEF) is a major health problem without effective therapies. This syndrome is rising in prevalence and is associated with high morbidity and mortality.

Purpose: To assess whether TYA-11631, a histone deacetylase 6 (HDAC6) selective inhibitor, improves cardiac structure and heart function in a novel mouse model of diastolic dysfunction with preserved ejection fraction.

Methods and Results: Surgically applying moderate trans-aortic constriction (mTAC) in wild type C57BL6 mice fed on high fat diet (HFD) induces a cardio-metabolic heart failure phenotype that recapitulates systemic and cardiovascular features of HFpEF in human. After the HFpEF phenotypes were established, animals were dosed orally with 30 mg/kg TYA-11631 or vehicle once per day for six weeks. This treatment regimen significantly reduced left ventricular (LV) mass, LV wall thickness, and improved glucose tolerance. In addition, TYA-11631 treatment sustained improved LV relaxation and LV filling pressures as shown by decreased prolongation of isovolumetric relaxation time, lower E/A and E/e' ratios, improved e' velocity, and reduced end diastolic pressure. Each of these efficacy parameters were normalized to control levels. Furthermore, HFD/mTAC mice treated with TYA-11631 showed a trending decrease in lung weight, indicating improved pulmonary congestion, consistent with reduced filling pressure. No treatment related adverse events or toxicities were observed in the animals in the study. At molecular level, TYA-11631 significantly inhibited upregulation of genes commonly associated with fibrosis (Postn, Col1a1, Col3a1, Col5a2), cardiac stress (Nppb), and inflammation (Tnfα) in heart tissue of HFD/mTAC mice.

Conclusion: Our results suggest that selectively inhibiting HDAC6 reverses a number of adverse pathophysiological processes in a HFD/mTAC mouse model of HFpEF. TYA-11631 holds promise as an effective therapeutic for the treatment of HFpEF in humans.