Abstract: P5995

A novel biased S1P1 agonist improves renal and cardiac functions in ZSF1 rats, a model of metabolic syndrome-associated Heart Failure with preserved Ejection Fraction

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Topic(s):
Heart Failure with Preserved Ejection Fraction

Citation:
Background/Introduction: Heart Failure with preserved ejection fraction (HFpEF) is a major cause of death worldwide with currently no approved treatment. Diastolic dysfunction, dyspnea, intolerance to effort, high cardiac filling pressure, and lung congestion coexist with normal ejection fraction in this clinical syndrome. Ageing, obesity, type 2 diabetes, hypertension and renal dysfunction are the main comorbidities found in this heterogeneous group of patients. Microvascular endothelial dysfunction, driven by these risk factors, may be a common link with other aspects of the HFpEF pathogenesis that include oxidative stress, inflammation, cardiomyocyte stiffness/hypertrophy, and myofibroblast accumulation. Sphingosine-1-phosphate type-1 receptor (S1P1), a G protein–coupled receptor highly expressed in endothelial cells, regulates vascular integrity, vascular development and immune cell trafficking. Compound A is a novel G protein-biased S1P1 agonist that lacks functional antagonism and has endothelial-protective properties.

Purpose: S1P1 activation could promote phosphorylation of endothelial nitric oxide synthase, restoration of endothelial structure and function, and thus diminish cardiac and vascular stiffness, hypertrophy and fibrosis. The aim of this study was to investigate if compound A could improve renal and cardiac functions in a rat model of HFpEF with metabolic syndrome.

Methods: 65-week-old obese ZSF1 rats were fed a chow diet containing compound A (8 mg/kg/day) or no compound for 4 weeks. Lean ZSF1 and Wistar rats were included in the study as control groups. Urinary protein/creatinine ratio was measured as an index of glomerular injury. Cardiac hypertrophy and function were assessed by two-dimensional and Doppler echocardiography. Total cardiac and atrial weights and pulmonary edema were assessed.

Results: The obese ZSF1 rat was confirmed as a relevant model of HFpEF with advanced renal dysfunction. These rats showed severe glomerular filtration impairment, left ventricular and atrial hypertrophy and pulmonary edema. Cardiac systolic function, cardiac output and chamber volumes were preserved, diastolic function was impaired, and left ventricular posterior walls and septal thicknesses were increased compared to control groups. Four weeks of compound A treatment reduced urinary protein/creatinine ratio, blunted cardiac and atrial hypertrophy, and partially restored diastolic function. Circulating lymphocytes were not reduced by compound A, confirming that these pharmacological effects were not associated with S1P1 desensitization.

Conclusion: Compound A, a novel S1P1 agonist with endothelial properties, improves cardiac and renal functions in a rat model of metabolic syndrome-associated HFpEF. Sustained S1P1 activation with compound A may be a promising strategy for HFpEF treatment.