DPP-4 inhibition by Linagliptin prevents cardiac inflammation, fibrosis, hypertrophy, and stiffness in obese ZSF1 rats.

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Introduction: More than half of the heart failure (HF) patients have a normal cardiac systolic function at rest – referred to as HF with preserved ejection fraction (HFrEF). Importantly, because of the increasing aging, obese and type 2 diabetic population, the prevalence of HFrEF is rising at an alarming rate while prevention and treatment strategies are absent.

Purpose: As the anti-diabetic drug Linagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, has cardioprotective effects, we hypothesized that Linagliptin could protect against cardiac inflammation, fibrosis, hypertrophy, and stiffness in obese ZSF1 rats, a metabolic risk-induced HFrEF model.

Methods: Sixteen weeks old obese ZSF-1 rats – having combined obesity, hypertension and type 2 diabetes – received Linagliptin supplemented diet (83 mg/kg; n=7) or placebo chow (n=7) for four weeks, while hypertensive non-diabetic Lean ZSF-1 rats, which do not develop HFrEF, served as non-diseased controls (n=5).

Results: Linagliptin significantly reduced plasma DPP4 activity (-81.9%), elevated active glucagon-like peptide 1 (+217.3%; inhibited by DPP4), and thereby improved glucose tolerance (AUC -20%) in obese ZSF1 rats proving its anti-diabetic effects. In addition, Linagliptin ameliorated the metabolic syndrome in obese ZSF1 rats as reflected by significantly diminished total body weight (-11.5%), individual organ (liver, spleen, kidney) weight to tibia length, plasma triglycerides (-51.8%) and non-HDL cholesterol levels (-31.2%), and elevated plasma HDL levels (+75.0%). Furthermore, Linagliptin significantly reduced cardiac leukocyte infiltration (-31.6%), while inducing a trend towards reduced systemic (pro-inflammatory) monocyte levels (-33.9%; p=0.08) in obese ZSF1 rats suggesting that Linagliptin has cardiac and systemic anti-inflammatory effects. Moreover, Linagliptin significantly reduced perivascular fibrosis (-27.7%) indicating its anti-fibrotic effect. In addition, Linagliptin prevented microvascular rarefaction (+52.80%) and reduced cardiac H2O2 levels (-67.0%) proposing its vasoprotective effect. Importantly, Linagliptin decreased cardiac hypertrophy as reflected by a significantly diminished left ventricular weight to tibia length (-9.0%) and a trend towards reduced cardiomyocyte size (-16.2%; p=0.05) in obese ZSF1 rats. Furthermore, Linagliptin prevented titin hypophosphorylation (+166.40%), specifically N2Bus s480 (+391.1%), thereby reducing the passive tension (-68.8%) ex vivo in isolated cardiomyocytes of obese ZSF1 rats. Finally, in vivo, Linagliptin improved left ventricular diastolic dysfunction as reflected by a 24.1% reduction in deceleration time, an indicator of left ventricular stiffness, in obese ZSF1 rats.

Conclusion: The anti-diabetic drug Linagliptin prevented cardiac inflammation, perivascular fibrosis, capillary
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