Non-steroidal mineralocorticoid receptor antagonist, finerenone, attenuates obesity- and hypertension-induced cardiomyocyte hypertrophy in a blood pressure-independent manner

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Funding Acknowledgements: Type of funding sources: Private company. Main funding source(s): Bayer Japan

Background: The FIGARO-DKD study revealed that the non-steroidal mineralocorticoid receptor antagonist (MRA), finerenone improved cardiovascular outcomes in patients with type 2 diabetes. The usefulness of MRA for heart failure with reduced ejection fraction (HFrEF) has been established, however, it is not clear for heart failure with preserved ejection fraction (HFpEF). Furthermore, pathophysiological mechanisms of HFpEF itself has not been clarified, and the mechanism of action of MRA based on the pathophysiology peculiar to HFpEF needs to be verified.

Purpose: The cardioprotective effects of finerenone were investigated using the HFpEF mouse model.

Methods: As an HFpEF mouse model, we used the 15 weeks combined stress model of obesity and hypertension. (Schiattarella et. al., Nature 2019). High fat diet ingestion and 0.5 g/L of Nω-nitro-L-arginine methyl ester (L-NAME) drinking were loaded. As a drug administration experiment, with combined stress for 10 weeks, placebo or 10 mg/kg/day finerenone was administered for the last two weeks. After loading, body weight, blood pressure, heart weight, myocardial cross-sectional areas (CSAs), and mitochondrial protein acetylation were evaluated.

Results: As previously reported, combined stress induced body weight (BW) gain and blood pressure (BP) elevation (BW: control 24.4±1.5 g, combined stress 32.5±5.2 g; P = 0.0007, systolic BP: control 100.6±11.5mmHg, combined stress 113.6±12.6mmHg; P = 0.026). Histological analysis revealed the significant enlargement of cardiomyocyte CSAs in the combined stress group (control 8.0±2.5 micron², combined stress 12.1±3.1 micron²; P<0.0001). In addition, we found mitochondrial protein acetylation (acetylated lysine; AcK) level, adjusted by ubiquinol-cytochrome c reductase, rieske iron-sulfur polypeptide 1 (UQCRFS1) was also enhanced in the combined stress model (AcK/UQCRFS1: control 1.0±0.3, combined stress 2.5±0.28; P = 0.0034). Subsequently, finerenone administration did not show remarkable reduction of systolic BP compared to the placebo group (placebo 144±34.3 mmHg, finerenone 135.8±13.4 mmHg; P = 0.63). However, histological analysis revealed significant reduction of cardiomyocyte CSAs in the finerenone group (placebo 8.7±1.7 micron², combined stress 7.9±1.2 micron²; P = 0.0247). Furthermore, mitochondrial protein hyperacetylation was also ameliorated in the finerenone group (AcK/UQCRFS1: placebo 2.4±0.3, finerenone 1.7±0.32; P = 0.044).

Conclusion: In the HFpEF murine model, finerenone improved cardiac hypertrophy independent of blood pressure. In addition, mitochondrial protein hyperacetylation, which involves mitochondrial dysfunction, was also alleviated by finerenone administration. Previous our work demonstrated that fatty acid stress hyperacetylated mitochondrial proteins and induced the mitochondrial dysfunction (Arima et. al., Nature Metabolism 2021). Our findings indicate that the cardioprotective effects of finerenone may also affect mitochondrial function.