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Empagliflozin improves cardiac function through the increased production of acetylcarnitine in a murine non-diabetic heart failure model

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Topic(s): Basic Science - Cardiac Diseases: Drugs, Drug Targets

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Background: Empagliflozin is a renal sodium glucose transporter 2 (SGLT2) inhibitor, thereby mediates its anti-diabetic effect via excretion of glucose into urine. EMPA-REG OUTCOME study, the first big randomized control trial of empagliflozin have shown significant reduction of mortality and hospitalization due to heart failure in diabetic patients. This trial hasn't only had a huge impact to cardiovascular field, but also raised a number of questions about underlying mechanisms. It is also uncertain about the efficacy of empagliflozin in non-diabetic heart failure. In this study, we aimed to elucidate the biological effects and its underlying mechanism of empagliflozin in a murine non-diabetic heart failure model.

Methods: We generated a heart failure murine model due to left ventricular (LV) pressure over load by performing transverse aortic constriction (TAC) operation to C57BL/6NCr mice. Two weeks after TAC operation we started empagliflozin administration mixed with diet at the ratio of 0.03% w/w. LV function was measured with echocardiography after administration of empagliflozin for two weeks (four weeks after TAC operation) and compared to a littermate control (no treatment) group. Then, heart samples were collected and subjected to further studies including metabolomic analysis. In-vitro studies including Seahorse Extracellular Flux Analyzer were also conducted with differentiated C2C12 cells and neonatal rat ventricular myocytes (NRVM).

Results: We found that empagliflozin treatment (Empa) significantly ameliorated LV systolic dysfunction induced by TAC compared to control group (Con) (figure.A) while heart weight/body weight ratio wasn't reduced. To explore key metabolites that can contribute to improvement of LV function, we conducted metabolomic analysis and found that empagliflozin significantly increased plasma acetylcarnitine level both in sham and TAC groups (figure.B). Previous studies have shown that acetylcarnitine acts as a substrate of acetyl CoA to fuel tricarboxylic acid cycle, and we tested the efficacy of acetylcarnitine for mitochondrial respiration capacity in differentiated C2C12 cells with Seahorse Extracellular Flux Analyzer. This analysis revealed that administration of acetylcarnitine resulted in a significant increase of oxygen consumption reflected by enhancing mitochondrial respiration. Similary, acetylcarnitine also markedly ameliorated impairment of mitochondrial respiration induced by isoproterenol in NRVM.

Conclusion: Our results indicated that empagliflozin has cardioprotective effect in murine heart failure model by enhancing mitochondrial respiration through the increased production of acetylcarnitine. We provide new evidence that empagliflozin would become a promising therapeutic agent to heart failure without diabetes.
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