

## MITOCHONDRIAL DYNAMICS UNBALANCE IN A MODEL OF CARDIAC HYPERTROPHY: EFFECT OF FENOFIBRATE TREATMENT

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**Introduction:** Pathological hypertrophy is the cardiac response to chronic pressure overload and leads to contractile dysfunction and heart failure. Accumulating evidence suggests that mitochondrial dysfunction and dysregulation of autophagy, a self-degradative processes that governs cellular homeostasis, as possible key players in cardiac hypertrophy. Mitochondrial integrity is maintained by a complex regulating network named "mitochondrial dynamics" and by mitophagy, the clearance process of mitochondria. Recent data show that fenofibrate, a peroxisome proliferator-activated receptor-alpha (PPAR- $\alpha$ ) agonist, reduces cardiac remodelling and improves cardiac function. The aim of this study is to evaluate the effects of fenofibrate on cardiac left ventricular (LV) hypertrophy, mitochondrial dynamics, mitophagy and autophagy in two-kidney one-clip (2K1C) rat. This is a model of renovascular hypertension and it is commonly used to mimic cardiac hypertrophy.

**Material and methods:** The Two-Kidney One-Clip (2K1C) protocol was applied to Wistar Kyoto male rats by placing a silver clip on the renal artery (n=15); sham operated rats were used as controls (2K0C, n=9). Four weeks after clipping, 2K1C animals were randomized to receive fenofibrate (150 mg/kg/day. 2K1C-FFB, n=8) or vehicle (2K1C-VEH, n=7), for eight weeks. At 12weeks after surgery, systolic pressure and cardiac functional parameters were assessed, by tail-cuff plethysmography and by cardiac magnetic resonance imaging (cMRI) respectively. Western blot and immunofluorescence/histological analyses were performed on cardiac tissue.

**Results:** Compared to sham-operated (2K0C) rats, 2K1C-VEH developed severe hypertension and a pathological cardiac remodelling with increased LV mass and relative wall thickness (RWT) in 2K1C-VEH rats, which were significantly reduced by FFB. The occurrence of cardiac hypertrophy in 2k1C-VEH was confirmed by fluorescence analysis of cross section area of LV cardiomyocytes stained with wheat-germ agglutinin. The protein expression of the regulators of mitochondrial dynamics as MFN2for fusion, Drp1for fission and Parkin for mitophagy was significant altered in 2K1C-VEH and re-balanced in 2K1C-FFB. The analysis of the expression of principal key regulators of autophagy revealed an increased LC3-II/LC3-I ratio in 2K1C-VEH and 2K1C-FFB, whereas showed an increase of Atg5and decrease of p62only in 2K1C-FFB.

**Discussion and conclusions:** Our results indicate that fenofibrate treatment counteracts pressure-induced cardiac maladaptive remodelling. The beneficial effects of fenofibrate could be ascribed to an enhanced autophagy, which reduces the hypertension-related detrimental mitochondrial effects leading to unbalanced mitochondrial dynamics.