Pioglitazone inhibits diabetes-induced atrial mitochondrial oxidative stress and improves mitochondrial biogenesis, dynamics and function through the PGC-1 signaling pathway

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Background: Oxidative stress contributes to adverse atrial remodeling in diabetes mellitus. This can be prevented by the PPAR-? agonist pioglitazone through its anti-oxidant and anti-inflammatory effects.

Purpose: In this study, the molecular mechanisms underlying these effects were investigated.

Methods: Rabbits were randomly divided into control (C), diabetic (DM), and pioglitazone-treated DM (Pio) groups. Echocardiographic, hemodynamic, electrophysiological, intracellular Ca2+ properties were measured. Serum PPAR-? levels, serum and tissue oxidative stress and inflammatory markers, mitochondrial morphology, reactive oxygen species (ROS) production rate, respiratory function, and mitochondrial membrane potential (MMP) levels were measured. Protein expression of pro-fibrotic marker transforming growth factor ß1 (TGF-ß1), and the mitochondrial proteins (PGC-1a, fission and fusion-related proteins) were measured.

Results: Compared with controls, the DM group demonstrated larger left atrial diameter and fibrosis area associated with a higher incidence of inducible AF. Lower serum PPAR-? level was associated with lower PGC-1a, higher NF-?B and higher TGF-ß1 expression. Mn-SOD protein was not different but lower mitochondrial fission- and fusion-related proteins were detected. Mitochondrial swelling, higher mitochondrial ROS, lower respiratory control rate, lower MMP and higher intracellular Ca2+ transients were observed. In the Pio group, reversal of structural remodeling and lower inducible AF incidence were associated with higher PPAR-? and PGC-1a. NF-?B and TGF-ß1 were lower and biogenesis, fission and fusion-related protein were higher. Mitochondrial structure and function, and intracellular Ca2+ transients were improved. In HL-1 cell line, transfected with PGC-1a siRNA blunted the effect of pioglitazone on Mn-SOD protein expression and MMP collapse in H2O2-treated cells.

Conclusion: Diabetes mellitus induces adverse atrial structural and electrophysiological remodeling, abnormal Ca2+ handling and mitochondrial damage and dysfunction. Pioglitazone prevented these abnormalities through the PPAR-?/PGC-1a pathway.