Mitochondrial ATP Sensitive Potassium Channel Opening Blocks Cardiac Hypertrophy by Preventing Oxidative Stress and Mitochondrial Damage

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INTRODUCTION. Pathological cardiac hypertrophy is characterized by a wall thickening or chamber enlargement of the heart in response to pressure or volume overload, respectively. If sustained, this condition will impair the organ contractile function rendering dysfunctional mitochondria and triggering oxidative stress. Mitochondrial ATP sensitive K^+ channel (mitoKATP) opening is protective against several cardiac insults by mitochondrial protection and modulating the oxidative status of the cell. We have previously shown that activation of mitoKATP protects against isoproterenol-induced cardiac hypertrophy. **OBJECTIVES.** Here, we tested the hypothesis that mitoKATP opening (using diazoxide) will avoid isoproterenol-induced cardiac hypertrophy in vivo by decreasing Reactive Oxygen Species (ROS) production and mitochondrial Ca^{2+}-induced swelling. **MATERIALS AND METHODS.** To induce cardiac hypertrophy Swiss mice were treated intraperitoneally with isoproterenol (30 mg/kg/day) for 8 days. Diazoxide (5 mg/kg/day) was used for opening of the mitoKATP and 5-hydroxidecanoate (5 mg/kg/day) was administrated as a mitoKATP blocker. Mitochondria were isolated by differential centrifugation. Hydrogen peroxide (H_2O_2) released by ventricular (50 mg) blocks, incubated with amplex red (Molecular Probes, 50 µmol/L) and horseradish peroxidase (1 U/mL) for 30 min at 37 °C, was detected spectrophotometrically (560 nm). Optical density (520 nm) decreases over time was used to detect changes in light scattering due to mitochondrial Ca^{2+} uptake and swelling. **DISCUSSION AND RESULTS**. Heart weight/body weight and heart weight/tibia length were elevated in mice treated with isoproterenol. Hypertrophic hearts had higher production of H_2O_2. On the other hand, MitoKATP opening with diazoxide reversed the H_2O_2 release in a manner reversed by 5-hydroxidecanoate. This beneficial effect was accompanied by lower Ca^{2+}-induced mitochondrial swelling isolated from mice treated with diazoxide, an effect blocked by 5-hydroxidecanoate. **CONCLUSIONS**. Our results suggest a promising role for mitoKATP as a tool for combating mitochondrial oxidative damage induced by cardiac hypertrophy.

Keywords: Cardiac hypertrophy, Oxidative stress, mitochondria