Mitochondrial ATP Sensitive Potassium Channel Opening Blocks Cardiac Hypertrophy by Augmenting Antioxidant Defenses


INTRODUCTION
Pathological cardiac hypertrophy is a chronic, complex disease that predominantly occurs in response to increased workload. After an initial phase of compensation, this condition will negatively impact contractile function causing mitochondrial dysfunction and often resulting in oxidative stress. On the other hand, the interplay between the opening of the mitochondrial ATP sensitive K+ channel (mitoKATP) and cardiac hypertrophy is poorly investigated.

OBJECTIVES
In this study we investigated the effect of mitoKATP opening (using diazoxide) on isoproterenol-induced cardiac hypertrophy in vivo.

MATERIALS AND METHODS
We used isoproterenol (30 mg/kg/day) for 8 days to induce cardiac hypertrophy in Swiss mice, diazoxide (5 mg/kg/day) for opening of the mitoKATP, 5-hydroxidecanoate (5 mg/kg/day) and glibenclamide (3 mg/kg/day), as mitoKATP blockers. Glutathione and protein thiol levels were detected using their reaction with DTNB. The catalase and glutathione peroxidase activity were detected following changes in H2O2 (240 nm) and NADPH (340 nm) absorbances, respectively, for 5 min. Superoxide dismutase activity was determined by following spectrophotometrically by the reduction of nitro blue tetrazolium to the blue formazan.

DISCUSSION AND RESULTS
Swiss mice treated with isoproterenol had elevated cellular protein levels, heart weight/body weight and heart weight/tibia length relationships. Isoproterenol-induced hypertrophy significantly suppressed the reduced protein thiol and total reduced glutathione, and impaired catalase, total superoxide dismutase activity and glutathione peroxidase. MitoKATP opening with diazoxide significantly prevented cardiac hypertrophy and normalized the levels of protein thiol and reduced glutathione. In addition, this treatment rescued the glutathione peroxidase and superoxide dismutase activity. On the other hand, diazoxide had no effect on catalase activity suppression. Finally, the protective effects of diazoxide were mitigated by the mitoKATP blockers 5-hydroxidecanoate and glibenclamide.

CONCLUSIONS
Taken together, these results clearly suggest that mitoKATP opening prevents oxidative stress during isoproterenol-induced cardiac hypertrophy and provides new biochemical insights into the prevention and treatment of cardiac hypertrophy.

Keywords: Cardiac hypertrophy, Oxidative stress, mitochondria

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