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INHIBITION OF BETA1-ADRENERGIC RECEPTOR-CAMKII ACTIVATION BY INSULIN TREATMENT IMPROVES PROLONGED POST-ISCHEMIC CARDIAC REMODELING AND FUNCTION

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Objectives Chronic β1-adrenergic receptor (β1-AR)-calcium/calmodulin-dependent protein kinase II (CaMKII) activation leads to Ca^{2+} handling disturbances and adverse cardiac remodeling. We have previously demonstrated that insulin treatment exerts anti-apoptotic and prosurvival effects on myocardial ischemia/reperfusion. This study attempted to determine whether insulin treatment influences the prolonged ischemic cardiac remodeling and function and the underlying mechanisms.

Methods Myocardial infarction (MI) was induced by left coronary artery ligation in adult male rats. Sham and MI rats were randomly treated with saline, insulin (2 U/kg/d, hypo. daily), or insulin plus wortmannin (a PI3K inhibitor) for 4 wks.

Results At the end of four weeks after the ischemia surgery, MI rats receiving insulin treatment showed increased cardiac ejection fraction (46.9 %±1.5 % vs 37.4%±2.4 %, $p<0.05$), left ventricular developed pressure (LVDP) and positive maximal values of the first derivative of left ventricular pressure (+LV dP/dt_{max}) compared with those in saline group. Insulin-treated rats also showed a smaller LV cavity and thicker systolic interventricular septum. Although the general size and weight of heart were similar among four groups, the myocyte cross-sectional area was significantly increased in both saline and insulin groups. The pathologic hypertrophy-related proteins were decreased in insulin group (β-MHC, BNP, and ANP, all $p<0.05$). Moreover, insulin-treated rats showed increased PI3K p110 expression and Akt phosphorylation, and significantly decreased phosphorylation of phospholamban (Thr 17) and CaMKII both in basal and isoproterenol (ISO)-stimulated myocardial tissue ($p<0.05$). Importantly, inhibition of insulin signaling with wortmannin not only blocked insulin's inhibition of CaMKII, but also abolished the effects of insulin on cardiac structure and function (all $p<0.05$).

Conclusion Chronic insulin treatment promotes physiological hypertrophy and restrains pathological hypertrophy and consequently improves prolonged function in post-ischemic hearts. This may, at least partially, be attributed to the inhibition of β1-AR-CaMKII activation by insulin-stimulated PI3K-Akt signaling.

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