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, hyp. 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.