**EARLY INSULIN TREATMENT AMELIORATES POST-MI HEART FAILURE BY INHIBITION OF MYOCARDIAL CAMKII AND P38 MAPK ACTIVITY**

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Objectives: Insulin exerts anti-apoptotic and prosurvival effects in acute myocardial ischemia/reperfusion (MI/R). The present study investigated the long-term effects of insulin in the rat model of ischemic heart failure.

Methods: Heart failure was induced by subjecting rats to permanent ligation of the left coronary artery for 4 wks. Rats were then randomized to receive one of the following treatments after MI: saline (hypo. daily for 7 days), insulin (0.5 U/kg/d, hypo.), or insulin plus wortmannin (15 ug/kg/d i.v. 15 min before each insulin administration).

Results: Compared with saline group, insulin treated rats showed increased cardiac ejection fraction and +LV dp/dtmax (P<0.05). Moreover, insulin significantly decreased mRNA levels of beta-MHC, alpha-SKA, ANP and BNP 4 wks after MI. Furthermore, at the end of 7 days, insulin-treated rats showed increased PI3Kp110 expression and Akt and GSK3beta phosphorylation in peri-infarct-area (P<0.05). Importantly, the phosphorylation of calcium/calmodulin-dependent protein kinase II (CaMKII), and its down-stream target phospholamban (PLBThr17), decreased significantly in insulin group (P<0.05). Moreover, insulin also reduced p38MAPK phosphorylation. Inhibition of PI3K with wortmannin not only blocked insulin's inhibition of phosphorylation of CaMKII, PLBThr17, and p38MAPK, but also blunted the effects of early insulin treatment on post-MI cardiac function (P<0.05).

Conclusion: The present study shows that early insulin treatment enhances long-term post-MI cardiac function which partly due to inhibition of CaMKII and p38MAPK activity by stimulating PI3K-Akt activation. Insulin may be of therapeutic benefit in the treatment of ischemia-induced heart failure.