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INSULIN IMPROVES POST-ISCHAEMIC CARDIAC STRUCTURAL AND FUNCTIONAL CHANGES VIA INHIBITING P38 MAPK ACTIVATION AND THUS INCREASING PLASMA BNP LEVEL

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Objectives Insulin has been shown to possess cardioprotective effect in acute myocardial ischaemia/reperfusion (MI/R). The present study attempted to test whether long term insulin treatment influences adverse prolonged post-ischaemic cardiac structural

and functional changes and to further investigate the underlying mechanisms.

Methods Adult male rats were subjected to left anterior descending coronary artery occlusion and were randomised to receive one of the following treatments: saline (4 ml/kg/h i.v. injection beginning 10 min before the ischaemia and continuing for 2 h), insulin (60 U/l, i.v. injection following the same routine, and hypodermic injection of insulin (0.5 U/ml, 1 ml/kg/d) for 4 weeks after the ischaemia surgery), insulin plus a PI3K/Akt inhibitor wortmannin (15 mg/kg i.v. injection 15 min before each insulin administration), or insulin plus a p38 MAPK inhibitor SB239063 (0.5 mg/kg following the same routine).

Results At the end of 4 weeks after the ischaemia surgery, MI rats receiving long term insulin treatment showed smaller systolic left ventricle cavity (LVs) and thicker systolic interventricular septum (IVS), and increased cardiac ejection fraction (EF), left ventricular development pressure (LVDevP) and the instantaneous first derivation of left ventricle pressure ($\pm LV \text{ dP/dt}_{\text{max}}$) (all $p < 0.05$ vs saline). Moreover, the insulin treatment significantly increased Akt but inhibited p38 MAPK phosphorylations, and increased the plasma brain natriuretic peptide (BNP) level though it did not change the BNP mRNA expression. These cardioprotective effects of insulin and its effect on BNP were not blocked by the PI3K/Akt inhibitor wortmannin, and could not be further strengthened by the p38 MAPK inhibitor SB239063 (all $p < 0.05$).

Conclusions These data indicate that insulin improves post-ischaemic cardiac structural and functional changes via inhibiting p38 MAPK activation and thus increasing plasma BNP level.