Diabetes mellitus abrogates erythropoietin-induced cardioprotection against ischemic-reperfusion injury by alteration of the RISK/GSK-3β signaling

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Résumé en anglais	Recent studies reported cardioprotective effects of erythropoietin (EPO) against ischemia–reperfusion (I/R) injury through activation of the reperfusion injury salvage kinase (RISK) pathway. As RISK has been reported to be impaired in diabetes and insulin resistance syndrome, we examined whether EPO-induced cardioprotection was maintained in rat models of type 1 diabetes and insulin resistance syndrome. Isolated hearts were obtained from three rat cohorts: healthy controls, streptozotocin (STZ)-induced diabetes, and high-fat diet (HFD)-induced insulin resistance syndrome. All hearts underwent 25 min ischemia and 30 min or 120 min reperfusion. They were assigned to receive either no intervention or a single dose of EPO at the onset of reperfusion. In hearts from healthy controls, EPO decreased infarct size (14.36 ± 0.60 and 36.22 ± 4.20% of left ventricle in EPO-treated and untreated hearts, respectively, $p < 0.05$) and increased phosphorylated forms of Akt, ERK1/2, and their downstream target GSK-3β. In hearts from STZ-induced diabetic rats, EPO did not decrease infarct size (32.05 ± 2.38 and 31.88 ± 1.87% in EPO-treated and untreated diabetic rat hearts, respectively, NS) nor did it increase phosphorylation of Akt, ERK1/2, and GSK-3β. In contrast, in hearts from HFD-induced insulin resistance rats, EPO decreased infarct size (18.66 ± 1.99 and 34.62 ± 3.41% in EPO-treated and untreated HFD rat hearts, respectively, $p < 0.05$) and increased phosphorylation of Akt, ERK1/2, and GSK-3β. Administration of GSK-3β inhibitor SB216763 was cardioprotective in healthy and diabetic hearts. STZ-induced diabetes abolished EPO-induced cardioprotection against I/R injury through a disruption of upstream signaling of GSK-3β. In conclusion, direct inhibition of GSK-3β may provide an alternative strategy to protect diabetic hearts against I/R injury.
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