GW23-e0507

POLY(ADP-RIBOSE) POLYMERASE INHIBITOR REDUCES HEART ISCHAEMIA/REPERFUSION INJURY VIA INFLAMMATION AND AKT SIGNALLING

doi:10.1136/heartjnl-2012-302920a.105

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Objectives Poly (ADP-ribose) polymerase (PARP) has been proposed to play an important role in the pathogenesis of heart ischaemia/reperfusion (I/R) injury. 3,4-dihydro-5-[4-(1-piperidinyl)butoxy]-1(2H)-isoquinolinone (DPQ), a novel, potent PARP inhibitor, has been proved to have cardiac protective effects. However, the underlying mechanisms are still not thoroughly understood. In this study, we investigate the effect of DPQ on heart I/R injury and its potential mechanisms.

Methods Studies were performed with I/R rats' hearts. DPQ was used to inhibit the activate of PARP. The myocardial infarction size, cardiac function and cells apoptosis were detected. The

activation of PARP, transcription factor nuclear factor-kappaB (NF-κB), intercellular adhesion molecule-1 (ICAM-1), cyclooxygenase-2 (COX-2) and Matrix metalloproteinase-9 (MMP-9) were evaluated during the I/R protocol.

Results Our data showed that DPQ could reduce the rat heart I/R injury in vivo. Heart I/R caused a significant increase in PARP activity. Administration of DPQ could decrease the activation of PARP. At the same time, administration of DPQ could decrease myocardial infarction size from 60.97±4.22% to 39.03±3.94% ($p<0.05$) and cells apoptosis from 35±5.3% to 20±4.1% ($p<0.05$) and simultaneously improved the cardiac function. In addition, we found that DPQ reduced the expression of NF-κB, ICAM-1, COX-2 and MMP-9 in rat heart. At the same time, DPQ facilitated Akt activation and decreased the activity of its downstream target, glycogen synthase kinase-3β (GSK-3β) and the forehead transcription factor FOXO3a.

Conclusions Our results suggested that the inhibition of PARP was able to reduce heart I/R injury. The protective effects of DPQ were associated with both inflammation and Akt signalling.