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VASONATRIN PEPTIDE ATTENUATES MYOCARDIAL ISCHAEMIA/REPERFUSION INJURY THROUGH INHIBITING THE ENDOPLASMIC RETICULUM STRESS AND THUS ENHANCING THE CELL SURVIVAL SIGNALS IN DIABETIC RATS

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Objectives People with diabetes mellitus (DM) have a risk of ischaemic heart disease (IHD) two to five times greater than that in

nondiabetic individuals. Diabetic patients have significantly more severe and fatal myocardial infarctions than nondiabetic patients. Thus therapies for treating myocardial ischaemia/reperfusion (MI/R) have recently attracted considerable attention. It is known that atrial natriuretic peptide (ANP) and C-type natriuretic peptide (CNP) significantly reduces the MI/R damage in normal rats. Vasonatrin peptide (VNP) is an artificial synthetic chimera of ANP and CNP, however, the effects of VNP on acute MI/R injury, especially in patients with diabetes, were still unclear. This study was designed to investigate the effects of VNP on MI/R-induced cells injury (necrosis and apoptosis) and heart function in diabetic rats, and further study its underlying mechanisms.

Methods The high-fat diet-fed streptozotocin (HFD-STZ) rat model (type 2 DM model) was developed. Age- and gender-matched normal and DM rats were subjected to 30 min of myocardial ischaemia and 4 h of reperfusion.

Results Compared with the normal control, DM rats showed more severe myocardial functional impairment and injury. Treatment of DM rats with VNP (100 μg/kg i.v.) significantly improved the instantaneous first derivation of left ventricle pressure (±LV dP/dt_{max}, (2842±103) and -(2531±79) mm Hg/s vs (2636±90) and -(2422±83) mm Hg/s in DM group, n=8), reduced infarct size ((43.32±8.15) % vs (53.46±10.15) %), plasma creatine kinase and lactate dehydrogenase activities, and apotosis ((36.0±6.1) % vs. (45.7±7.5) %) at the end of reperfusion (all $p<0.05$). After demonstrating that VNP attenuated MI/R injury in DM model, we further investigated the underlying mechanisms.

MI/R induced obvious endoplasmic reticulum (ER) stress in DM myocardium as evidenced by increased GRP78 and Chop levels. VNP significantly reduced the expression of these ER stress-related proteins (n=3, $p<0.05$), and consequently increased the antiapoptotic protein Akt and ERK1/2 expression and phosphorylation levels ($p<0.05$). VNP's both effects on proteins and myocardial injury were mimicked by cGMP (mediating VNP signalling) analogues 8-Br-cGMP (1 mg/kg, i.p., 20 min before reperfusion), whereas inhibited by selective PKG inhibitor KT-5823 (0.5 mg/kg, i.p.) (both $p<0.05$). In addition, pretreated DM rats with ER stress inhibitor TUDCA (50 mg/kg, i.p.) couldn't further promote the VNP's both effects of increasing antiapoptotic proteins and cardioprotection ($p>0.05$).

Conclusions VNP treatment confers cardioprotection in MI/R by inhibiting the endoplasmic reticulum stress and consequently enhancing the cell survival signalling Akt and ERK1/2 in diabetic rats. These results suggest that VNP may act as an insulin sensitiser and have potential therapeutic value for the diabetic patients with ischaemic heart disease.