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Nitrotyrosine and iNOS as Biomarkers in Doxorubicin Induced Cardiotoxicity. The Preventive and Therapeutic Effect of the Natural Olive Product Oleuropein

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INTRODUCTION

Oleuropein (oleu) is a natural phenolic antioxidant, which is present in elevated concentration in olives, olive oil and oil leaves. Despite that oxidative stress is mainly involved in doxorubicin (DXR) induced cardiotoxicity, the exact mechanism is not yet fully elucidated. High concentration of NO achieved through the iNOS induction and peroxynitrite formation may participate in the DXR induced cardiotoxicity. The aim of the present study was to evaluate if iNOS and nitrotyrosine involved in the acute cardiotoxicity of DXR and the preventive and therapeutic effect of oleu in vivo.

METHODS

Fifty rats were divided into 6 groups and treated with saline, DXR (20 mg/kg, i.p) and DXR + oleu (100 or 200 mg/kg/BW i.p.) 2 days before and 2 days after DXR or only 2 days after the DXR administration. Three days after the end of DXR administration blood samples were taken for CPK, CPK-MB, LDH, ALT and AST assessment and the rats were sacrificed. Hearts were rapidly excised and immediately immersed into liquid nitrogen for tissue evaluation of lipid peroxidation indices (malondialdehyde MDA, and conjugated dienes CDs), protein carbonyl content (PCs), nitrotyrosine determination (NT) and immunostochemical evaluation of iNOS.

RESULTS

The DXR induced cardiotoxicity manifested biochemically by a significant elevation of serum CPK, CPK-MB, LDH, ALT and AST ($P<0.005$ vs saline). Oleu at both doses tested and both treatment modes (before and after or only after DXR administration) reduces the elevated by DXR levels of CPK, CK-MB, LDH, ALT and AST ($P<0.05$). Moreover, it reduces the DXR induced lipid peroxidation, and PCs content. NT concentration and iNOS induction were significantly elevated in the group treated with DXR. Oleu at both doses and both schemes reduced significantly the NT content and the iNOS induction in the myocardial tissue ($P<0.001$).

CONCLUSION

DXR acute cardiotoxicity produced a significant induction in iNOS and NT formation in the myocardium. Oleu has protective and therapeutic effect against DXR induced cardiotoxicity as it is expressed by the restoration of intracellular and peripheral markers of toxicity. Combined oleu-DXR treatment may improve the therapeutic outcome by eliminating the undesirable cardiotoxicity.