MO-01

The protective effect of recombinant human paraoxonase 1 subtype K192 against organophosphate poisoning in myocardial injury

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Objective: In recent years, the studies found that paraoxonase (PON1) can hydrolyze organophosphorus compounds as a member of the phosphotriesterase family. Exogenous PON1 obtained through gene recombination has been applied in animal experiments, which confirmed that it increases the tolerance against organophosphate in rats. Studies have shown that the 192nd site of PON1 amino acid sequence is the key point to determine the enzymatic activity. PON1 expresses better thermal stability, better catalytic ability and wider organophosphate hydrolysis spectrum in rabbit with lysine (K192) than humans, rodents and poultry. In this experiment we use the recombinant human $PON1_{K192}$ ($rHuPON1_{K192}$) through the expression of E. Coli. applied it to the rats exposure to organophosphate. We try to explore the mechanism of PON1 against organophosphate poisoning through observing its protective effect on the myocardial tissues, thus provide a theoretical and experimental basis for prevention and treatment of organophosphate poisoning.

Methods: After injection of $rHuPON1_{K192}$ (9000U/kg) 30 minutes ahead of the exposure to chlorpyrifos (organophosphorus pesticide), SD rats accepted intragastric administration at a dose of (2LD50). 8h later, serum cardiac troponin (cTnI) and creatine phosphate kinase isoenzyme (CK-MB) were tested; Left ventricular myocardial tissue was taken under light microscope and transmission electron microscopy to observe the myocardial cells and their ultrastructural changes. We also observed the myocardial Bax and Bcl-2 expression through immunohistochemical method. All of above were analyzed and compared with the chlorpyrifos group and the control group.

Results: The serum cTnI and CK-MB were significantly decreased in chlorpyrifos group compared with $rHuPON1_{K192}$ pretreatment group (the difference was statistically significant). Under the light microscope and electron microscope the control group showed normal myocardial cells. The signs of myocardial cell swelling, inflammatory cells infiltration, interstitial vasodilation, muscle bundle structure sparse and arranged disorderly, even myocardial hemorrhage can be seen under light microscope in chlorpyrifos group. Myocardial tissue ultrastructure under electron microscope showed damage obviously: myocardial cell swelling, mitochondria swelling and crista arranged disorderly, partial or whole mitochondrial crista dissolved with cavity left. In $rHuPON1_{K192}$ pretreatment group, myocardial cells showed slight swelling with muscle bundle orderly arrangement, a few inflammatory cells infiltration without hemorrhage and necrosis. Myocardial fiber structure by electron microscopy is basic normal with mild swelling of mitochondria. The $rHuPON1_{K192}$ group obviously reduced myocardial damage. Bax and Bcl-2 expression of chlorpyrifos group were significantly increased, and Bax/Bcl-2 ratio was higher than that of the control group obviously (the difference was statistically significant). Bax and the Bcl-2 expression had also increased in the $rHuPON1_{K192}$ pretreatment group than that of the control group, but the Bax/Bcl-2 ratio had a downward trend in the $rHuPON1_{K192}$ pretreatment group (the difference was statistically significant).

Conclusion: $rHuPON1_{K192}$ can relieve myocardial injury from acute chlorpyrifos poisoning, lower ratio of apoptosis related gene Bax/Bcl-2, thus improve heart pathological morphology with myocardial protection.