Research in Pharmaceutical Sciences, 2012;7(5)
School of Pharmacy and Pharmaceutical Sciences
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Thallium induces mitochondrial permeability transition pore opening and cytochrome C release: oxidative stress mechanisms

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Background and Aims: Thallium (Tl) is a highly toxic heavy metal though up to now its mechanisms are poorly understood. In previous studies, we showed that this compound could induce reactive oxygen species (ROS) formation, GSH oxidation, membrane lipid peroxidation and mitochondrial membrane potential in isolated rat hepatocyte. Since the liver is the storage site in thallium toxicity, it seems that the mitochondria are one of the most important targets for hepatotoxicity. Aims: In the present work, we studied the effects of thallium on mitochondria to investigate the mechanisms of toxicity.
Methods: Mitochondria were isolated from rat liver and incubated with different concentration of Tl (25-200 μM).
Results: Our studies indicated that Tl (25-200 μM) could induce mitochondrial swelling in a concentration dependent manner and disrupt mitochondrial membrane potential in a time dependent manner, which is quite different from the rapid ΔΨ collapse caused by Ca2+ before mitochondrial swelling ensued. Decreased disturbance in oxidative phosphorylation was also shown by decreased ATP/ADP ratio. In addition, collapse of mitochondrial membrane potential (MMP), mitochondrial swelling and release of cytochrome c following thallium treatment well inhibited by pretreatment of mitochondria with CsA and BHT.
Conclusions: It concluded that this compound induced liver toxicity is the result of metals disruptive effect on liver hepatocyte mitochondrial respiratory chain which is the obvious cause of Tl+ induced ROS formation , lipid peroxidation, mitochondrial membrane potential decline and cytochrrome c expulsion which starts cell death signaling.

Keywords: Thallium (Tl); ROS formation; Mitochondrial membrane potential; Isolated mitochondria