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School of Pharmacy and Pharmaceutical Sciences
Isfahan University of Medical Sciences

Toxicity of Copper in isolated liver mitochondria: a new tool in re-approaching of the ethiology of $Cu2^{+}$ overloading liver diseases

M. Hosseini[1,*], J. Pourahmad[2], F. Shaki[3], M. Ghazi-Khansari[4]

[1]Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran and Department of Pharmacology and Toxicology, School of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran andFaculty of Pharmacy, Students Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran and Department of Pharmacology and Toxicology, School of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[4]Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Background and Aims: Copper (Cu2+)-induced oxidative damage has been implicated in disorders associated with abnormal metabolism and also neurodegenerative diseases. Previously, we showed that the Cu2+ 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 and also important target organ in Cu2+ toxicity, it seems that the mitochondria are one of the most important targets for Copper hepatotoxicity. Aims: The mitochondriotoxicity mechanism of Cu2+, an essential redox transition metal was investigated in isolated rat liver mitochondria.
Methods: Isolated rat liver mitochondria were obtained by differential ultracentrifugation and the isolated rat liver mitochondria were then incubated with different concentrations of Cu2+ (10-60µm).
Results: Our results showed that Cu2+(10-60µm) induced a concentration and time-dependent rise in mitochondrial ROS formation, lipid peroxidation and mitochondrial membrane potential collapse before mitochondrial swelling ensued. Decreased disturbance in oxidative phosphorylation was also shown by decreased ATP concentration and decreased ATP/ADP ratio in Cu2+-treated isolated mitochondria. In addition, collapse of mitochondrial membrane potential (MMP), mitochondrial swelling and release of cytochrome c following copper treatment well inhibited by pretreatment of mitochondria with CsA and BHT.
Conclusions: Our results showed that Cu2+ could interact with respiratory complexes (I, II and IV). We finally concluded that Cu2+ induced liver toxicity is the result of metals disruptive effect on liver hepatocyte mitochondrial respiratory chain which is the obvious cause of Cu2+- induced ROS formation , lipid peroxidation, mitochondrial membrane potential decline and cytochrrome c expulsion which starts cell death signaling .

Keywords: Copper (Cu); ROS formation; Mitochondrial membrane potential; Isolated mitochondria