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Depleted Uranium induces disruption of energy hemostasis and oxidative stress in isolated rat brain mitochondria

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Background and Amis: Depleted uranium (DU), a byproduct of the enrichment process of uranium, is emerged as an environmental pollutant primarily due to its military applications. The central nervous system is the target of DU and recent evidence suggested that DU could induce oxidative stress and mitochondrial dysfunction in brain tissue. However, the underlying mechanisms of DU toxicity in brain mitochondria have not yet been well understood.
Methods: Brain mitochondria were obtained using differential centrifugation and were incubated with different concentrations of uranyl acetate (a soluble salt of U238) (50,100 and 200µM). In this research, mitochondrial ROS production, collapse of mitochondrial membrane potential and mitochondrial swelling was examined by flow cytometry following addition of uranyl acetate (UA). Meanwhile, mitochondrial sources of ROS formation were determined using specific substrates and inhibitors. Complex II and IV activity and also extent of lipid peroxidation and glutathione (GSH) oxidation were detected via spectroscopy. Furthermore, we investigated the concentration of ATP and ATP/ADP ratio using luciferase enzyme and release of cytochrome c from mitochondria which was detected by ELISA kit.
Results: UA caused concentration-dependent elevation of succinate-linked mitochondrial ROS production, lipid peroxidation, GSH oxidation and inhibition of mitochondrial complex II but showed no effect on mitochondrial complex IV. UA also induced mitochondrial permeability transition, ATP production decrease and increase in cytochrome c release. Furthermore, BHT pre-treatment significantly inhibited all the above mentioned toxic effects of UA.
Conclusions: This study suggests that mitochondrial oxidative stress and impairment of oxidative phosphorylation in brain mitochondria may play a key role in DU neurotoxicity

Keywords: Depleted uranium; Neurotoxicity; Isolated mitochondria; Oxidative phosphorylation; Oxidative stress