

Heavy Metal Induced Cell Necrosis: Involves Apoptosis Death Signals Initiated by Mitochondrial Injury

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ABSTRACT

Introduction: Severe industrial diseases result from the hepatic accumulation of mercury, cadmium or chromium in humans and on the other hand cadmium and dichromate and mercuric salts may induce lung or kidney cancer. Acute or chronic CdCl₂, HgCl₂ or dichromate administration induces hepatic and nephrotoxicity in rodents. Oxidative stress is often cited as a possible cause of metal induced cell death but the death signaling pathways involved have not yet been well investigated.

Method and Materials: To search for death signaling mechanisms we used accelerated cytotoxicity mechanism screening techniques (ACMS) on isolated rat hepatocytes as our cellular model.

Results: Adding the CdCl₂, HgCl₂ or K₂Cr₂O₇ to isolated hepatocytes caused a rapid increase in reactive oxygen species ("ROS") formation and a decline in mitochondrial membrane potential. Then lipid per-oxidation and cell-lysis ensued. Cytotoxicity was prevented by "ROS" scavengers and various inhibitors of the mitochondrial permeability transition (MPT) e.g. cyclosporin A, carnitine or trifluoperazine. Antioxidants prevented hepatocyte lysis induced by CdCl₂, K₂Cr₂O₇ but not HgCl₂.

Conclusion: Hepatocyte lysis was also prevented by various apoptosis inhibitors e.g. cycloheximide, dactinomycin and a tetrapeptide caspase 3 inhibitor which suggested that metal induced hepatocyte lysis involves apoptotic death signals initiated by MPT and "ROS".

Keywords: Chromium, Cadmium, Mercury, MPT, Lipid per oxidation, ROS, Apoptosis, Necrosis .

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