Abstract

Introduction: Mitochondrial toxicity has been shown to contribute to a variety of organ toxicities such as liver. Isolated mitochondria as high-throughput applicable screening assays has used to assess mitochondrial toxicity, prediction of organ toxicities and mechanistic investigations. Ifosfamide as an anticancer drug, is associated with increased risk of neurotoxicity, cardiotoxicity nephrotoxicity, hepatotoxicity and hemorrhagic cystitis. Due to the lack of complete information about the direct effect of IFO on mitochondrial function, the aim of this study was to evaluate the direct effect of IFO on isolated mitochondria obtained from liver.

Methods: Mitochondria were isolated with mechanical lysis and differential centrifugation form liver and treated with various concentrations of IFO (0, 5, 50, 100, 500, 1000 and 2000 µM). Using biochemical and flowcytometry assays we evaluated mitochondrial succinate dehydrogenases (SDH) activity, mitochondrial swelling, mitochondrial lipid peroxidation, reactive oxygen species (ROS) production and mitochondrial membrane potential (MMP) during 1 hour

Results: Our data showed that IFO did not cause deleterious alterations in mitochondrial functions, mitochondrial swelling, lipid peroxidation ROS formation and MMP collapse in mitochondria isolated from liver.

Conclusion: Altogether, the data of this study showed that IFO is not directly toxic in in mitochondria isolated from liver, and suggests that probably other pathways and metabolisms have role in the toxicity of this compound. Also, this study proved that mitochondria alone not play the main role in the toxicity of IFO, and suggests to reduce the toxicity of this drug, other pathways resulting in the production of toxic metabolites and should be considered.

Key words: Mitochondria, Ifosfamide, Prediction of toxicity, Mechanisms of toxicity