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School of Pharmacy and Pharmaceutical Sciences
Isfahan University of Medical Sciences

Molecular mechanism of isoniazid-induced mitochondrial toxicity

M. Ahadpour*, M. Hosseini, M. Eskandari

Department of Pharmacology and Toxicology, School of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran

Background and Aims: Isoniazid (isonicotinic acid hydrazide) is an anti-tuberculosis drug that introduced in the 1950s. It is still the most active agent against Bacillus Tuberculosis and is used both for the treatment and the prophylaxis of tuberculosis. Isoniazid can cause hepatotoxicity in 20% of patients that is usually associated with an inflammatory response. However the exact mechanisms behind the isoniazid hepatotoxicity have not yet been completely understood. The aim of this study was to evaluate the molecular mechanism of isoniazid toxcicity in isolated rat liver mitochondria.
Methods: Liver was isolated from anesthetized male Sprague Dawley rat. Then minced and homogenized in an ice bath. The mitochondria were isolated by two steps centrifugation of homogenate. Mitochondrial Protein concentration was normalized by Bradford protein assay. The effects of isoniazid on complex II activity were evaluated by MTT assay. In this test the tetrazolium salt MTT is converted into blue, insoluble formazan dye crystals, which have to be dissolved by a suitable extraction mixture. Analysis of mitochondrial swelling after isolated mitochondria was estimated by changes in light scattering as monitored spectrophotometrically at 540 nm.
Results: Our study indicated that isoniazid (25-200 µM) could interact with second complex of mitochondrial respiratory chain and inhibit its activity. We also showed that isoniazid could alter the mitochondrial function and induce mitochondrial swelling. This effect was independent of concentration.
Conclusions: It can be concluded that isoniazid may initiate its toxicity in mitochondria through the inhibition of second complex of electron transfer chain. This event triggers different pathways that finally cause swelling of mitochondria.

Keywords: Isoniazid; Mitochondrial toxicity; Isolated mitochondria; Rat liver