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Evaluation of sodium valproate toxic effects on swelling and mitochondrial respiratory chain

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Background and Aims: Sodium valproate is one of the widely used anticonvulsant drugs. There is some evidence of liver injury in some of drug consumers. Sodium valproate is the third most common xenobiotic suspected of causing death due to liver injury. It has been previously reported that the cytotoxicity of sodium valproate is mediated by mitochondria in rat liver. Since the molecular mechanism of hepatotoxicity is still unknown, we investigate the molecular mechanism of sodium valproate in isolated rat liver mitochondria. In this study we assessed toxic effects of sodium valproate on complex II (Succinate dehydrogenase) activity and mitochondrial swelling in isolated rat liver mitochondria.
Methods: Liver was isolated from anesthetized male Sprague Dawley rat and 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 sodium valproate on complex II activity were evaluated by MTT assay based on reduction of MTT to purple formazan. Sodium valproate-mediated swelling was estimated by changes in light scattering as monitored spectrophotometrically at 540 nm.
Results: The MTT assay showed that activity of complex II was inhibited by sodium valproate (25-200 μM). In addition our results showed that sodium valproate induced mitochondrial swelling in a concentration dependent manner.
Conclusions: It can be concluded that sodium valproate inducted liver toxicity is mediated by mitochondrial toxicity. We suggest that the inhibition of complex II in electron transfer chain is the first step in sodium valproate toxicity mechanism. Our results also showed that sodium valproate induce mitochondrial swelling that could lead to cell death through apoptosis or necrosis.

Keywords: Sodium valproate; Mitochondrial toxicity; Isolated mitochondria; Rat liver