Title:	Dithiothreitol abrogates the effect of arsenic trioxide on normal rat liver mitochondria and human hepatocellular carcinoma cells
Authors:	Paul, Manash K. (/jspui/browse?type=author&value=Paul%2C+Manash+K.)
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Abstract:	Arsenic trioxide (ATO) is a known environmental toxicant and a potent chemotherapeutic agent. Significant correlation has been reported between consumption of arsenic-contaminated water and occurrence of liver cancer; moreover, ATO-treated leukemia patients also suffers from liver toxicity. Hence, modulation of ATO action may help to prevent populations suffering from arsenic toxicity as well as help reduce the drug-related side effects. Dithiothreitol (DTT) is a well-known dithiol agent reported to modulate the action of ATO. Controversial reports exist regarding the effect of DTT on ATO-induced apoptosis in leukemia cells. To the best of our knowledge, no report illustrates the modulatory effect of DTT on ATO-induced liver toxicity, the prime target for arsenic. Mitochondria serve as the doorway to apoptosis and have been implicated in ATO-induced cell death. Hence, we attempted to study the modulatory effect of DTT on ATO-induced dysfunction of mammalian liver mitochondria and human hepatocellular carcinoma cell line (Hep3B). We, for the first time, report that ATO produces complex I-mediated electron transfer inhibition, reactive oxygen species (ROS) generation, respiration inhibition, and ATO-induced ROS-mediated mitochondrial permeability transition (MPT) opening. DTT at low concentration (100μM and less) prevents the effect of ATO-induced complex I-malfunctions. DTT protects mitochondria from ATO-mediated opening of MPT and membrane potential depolarization. DTT also prevented ATO-induced Hep3B cell death. Thus, at low concentrations DTT abrogates the effect of ATO on rat liver mitochondria and Hep3B cell line. Therefore, the present result suggests, that use of low concentration of dithiols as food supplement may prevent arsenic toxicity in affected population.
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