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Inhibition of gene expression of carnitine palmitoyltransferase I and heart fatty acid binding protein in cyclophosphamide and ifosfamide-induced acute cardiomyopathic rat models

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This study investigated whether cyclophosphamide (CP) and ifosfamide (IFO) therapy alters the expression of the key genes engaged in long-chain fatty acid (LCFA) oxidation outside rat heart mitochondria, and if so, whether these alterations should be viewed as a mechanism during CP and IFO-induced cardiotoxicity. Adult male Wistar albino rats were assigned to one of six treatment groups: Rats in group 1 (control) and group 2 (L-carnitine) were injected intraperitoneal (i.p.) with normal saline and L-carnitine (200 mg/kg/day), respectively, for 10 successive days. Animals in group 3 (CP group) were injected i.p. with normal saline for 5 days before and 5 days after a single dose of CP (200 mg/kg, i.p.). Rats of group 4 (IFO group) were received normal saline for 5 successive days followed by IFO (50 mg/kg/day, i.p.) for 5 successive days. Rats of group 5 (CP-carnitine supplemented) were given the same doses of L-carnitine as group 2 for 5 days before and 5 days after a single dose of CP as group 3. Rats of group 6 (IFO-carnitine supplemented) were given the same doses of L-carnitine as group 2 for 5 days before and 5 days concomitant with IFO as group 4. Immediately, after the last dose of the treatment protocol, blood samples were withdrawn and animals were sacrificed for biochemical and gene expression studies. Treatment with CP and IFO significantly decreased expression of hear fatty acid binding protein (H-FABP) and carnitine palmitoyltransferase I (CPT I) genes in cardiac tissues. Moreover, CP but not IFO significantly increased Acetyl-CoA Carboxylase (ACC) mRNA expression. Conversely, IFO but not CP significantly decreased mRNA expression of Malonyl-CoA Decarboxylase (MCD). Both CP and IFO significantly increased serum lactate dehydrogenase (LDH), creatine kinase isoenzyme MB (CK-MB), and malonyl-CoA content in cardiac tissues. Interestingly, carnitine supplementation completely reversed all the biochemical and gene expression changes-induced by CP and IFO to the control values, except CPT I mRNA and protein expression remained inhibited by IFO. Data from the current study suggest that: (1) CP and IFO therapy are associated with the inhibition of the expression of H-FABP and CPT I genes in cardiac tissues with the consequent inhibition of mitochondrial transport and oxidation of LCFA. (2) The progressive increase in cardiotoxicity enzymatic indices and the decrease in H-FABP and CPT I expression may point to the possible contribution of these genes in CP and IFO-induced cardiotoxicity. (3) L-carnitine prevents CP and IFO-induced cardiotoxicity via modulating the expression of genes engaged in fatty acid oxidation in the heart.

Biography

Mohamed M. Sayed-Ahmed is a Professor of Pharmacology, King Saud University, Saudi Arabia and he graduated from College of Pharmacy, Egypt in 1985. After that he joined the National Cancer Institute, Cairo University, Egypt and completed his master thesis. In 1994, he started his Ph.D. at College of Medicine, Duke University Medical Centre, North Carolina, USA. He spent three years investigating the mechanisms where by anti-cancer drugs interfere with carnitine system and how carnitine supplementation prevents chemotherapy-induced multiple organ failure. In 1997, he received his Ph.D. in Pharmacology from National Cancer Institute, Cairo University, Egypt. From 2004, he is working as the Professor in the Department of Pharmacology, College of Pharmacy, King Saud University.

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