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Dietary Vitamin E Decreases Doxorubicin-Induced Oxidative Stress Without Preventing Mitochondrial Dysfunction

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Abstract

Doxorubicin (DOX) is a widely prescribed antineoplastic and although the precise mechanism(s) have yet to be identified, DOX-induced oxidative stress to mitochondrial membranes is implicated in the pathogenic process. Previous attempts to protect against DOX-induced cardiotoxicity with α-tocopherol (vitamin E) have met with limited success, possibly as a result of inadequate delivery to relevant subcellular targets such as mitochondrial membranes. The present investigation was designed to assess whether enrichment of cardiac membranes with α-ocopherol is sufficient to protect against DOX-induced mitochondrial cardiotoxicity. Adult male Sprague-Dawley rats received seven weekly subcutaneous injections of 2 mg/kg DOX and fed either standard diet or diet supplemented with α-tocopherol succinate. Treatment with a cumulative dose of 14 mg/kg DOX caused mitochondrial cardiomyopathy as evidenced by histology, accumulation of oxidized cardiac proteins, and a significant decrease in mitochondrial calcium loading capacity. Maintaining rats on the α-tocopherol supplemented diet resulted in a significant (two- to four-fold) enrichment of cardiac mitochondrial membranes with α-tocopherol and diminished the content of oxidized cardiac proteins associated with DOX treatment. However, dietary α-tocopherol succinate failed to protect against mitochondrial dysfunction and cardiac histopathology. From this we conclude that although dietary vitamin E supplementation enriches cardiac mitochondrial membranes with α-tocopherol, either (1) this tocopherol enrichment is not sufficient to protect cardiac mitochondrial membranes from DOX toxicity or (2) oxidative stress alone is not responsible for the persistent mitochondrial cardiomyopathy caused by long-term DOX therapy.

Key Words: Adriamycin; doxorubicin; mitochondria; α-tocopherol; vitamin E; cardiotoxicity.

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Introduction

Doxorubicin (DOX; Adriamycin®) is a highly potent anthracycline antineoplastic widely prescribed for treating a variety of cancers including both solid tumors and