Nathaniel W. Revis and Nives Marusic, “Sequestration of $^{45}Ca^{2+}$ by Mitochondria from Rabbit Heart, Liver and Kidney after Doxorubicin or Digoxin/Doxorubicin Treatment”, Experimental and Molecular Pathology, Volume 31, Issue 3, Pages 440-451, 1979

Sequestration of $^{45}Ca^{2+}$ by Mitochondria from Rabbit Heart, Liver and Kidney after Doxorubicin or Digoxin/Doxorubicin Treatment

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Received 30 April 1979
Revised 24 July 1979
Available online 29 April 2004

Abstract

Doxorubicin, an antibiotic of the anthracycline group, has proven effective in treating a variety of malignant disorders. However, its use has been limited due to the cardiotoxic side effects which include myocardial necrosis that is characterized by mitochondrial calcification. The present studies were conducted to determine if treatment of rabbits with doxorubicin (an anthracycline) would affect the ability of mitochondria isolated from heart, liver, and kidney to retain $^{45}Ca^{2+}$. Increases in mitochondrial retention of $^{45}Ca^{2+}$ by all of the tissues studied were observed, although only that from the heart showed a significant increase. The changes in $^{45}Ca^{2+}$ retention and morphology (i.e., increased mitochondrial swelling and intra-mitochondrial calcium phosphate crystals) of heart mitochondria from doxorubicin-treated rabbits suggest that this anthracycline directly or indirectly affects mitochondrial flux of calcium. That liver and kidney (as compared to heart) mitochondria are relatively insensitive to the effects of doxorubicin suggests a chemical difference in the mitochondria isolated from these tissues. Digoxin/doxorubicin treatment of rabbits, however, leads to a decrease in mitochondrial retention of $^{45}Ca^{2+}$, except for hear tissue, which again was significantly increased over the control.2 The effects of this treatment on the Image activated ATPase of the heart, and on the accumulation of doxorubicin by the heart, were not significantly different from the control, suggesting that digoxin and doxorubicin do not compete for the same binding site.

Research sponsored by the Division of Biomedical and Environmental Research, U.S. Department of Energy under contract W-7405-eng-26 with the Union Carbide Corporation.