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Bile Acids Are Toxic for Isolated Cardiac Mitochondria

A Possible Cause for Hepatic-Derived Cardiomyopathies?

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Abstract

Cholestasis and other liver diseases may affect the heart through the toxic effects of the retained bile acids on cardiac mitochondria, which could explain the origin of hepatic-derived cardiomyopathies.

The objective of this work was to test the hypothesis that bile acids are toxic to heart mitochondria for concentrations that are relevant for cholestasis.

Heart mitochondria were isolated from rat and subjected to incubation with selected bile acids (litocholic acid [LCA], deoxycholic acid [DCA], chenodeoxycholic acid [CDCA], glycochenodeoxycholic acid [GCDC], taurodeoxycholic acid [TDCA], and glycoursodeoxycholic acid [GUDC]).

We observed that the most toxic bile acids were also the most lipophilic ones (LCA, DCA, and CDCA), inducing a decrease on state 3 respiration, respiratory control ratio, and membrane potential and causing the induction of the mitochondrial permeability transition. GUDC was the bile acid with lower indexes of toxicity on isolated heart mitochondria.

The results of this research indicate that at toxicologically relevant concentrations, most bile acids (mainly the most lipophilic) alter mitochondrial bioenergetics. The impairment of cardiac mitochondrial function may be an important cause for the observed cardiac alterations during cholestasis.

Key Words: Cardiac mitochondria; mitochondrial permeability transition; hepatic disease; cholestasis; bile acids.

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Introduction

Cholestasis, defined as impaired bile flow, occurs in many chronic human liver diseases. During this condition, many toxic hydrophobic bile salts normally secreted by the liver into bile are now accumulated inside the hepatocyte *(1)*. The accumulation of toxic hydrophobic bile salts is associated with liver failure, leading ultimately to biliary fibrosis and cirrhosis. A possible reason for hepatic dysfunction may be an increased production of reactive oxygen species *(2,3)*, or an increased susceptibility of hepatocytes to apoptotic cell death *(4)*, that may well include damage to mitochondria. Hepatic mitochondrial membrane perturbations