Liver Mitochondrial Dysfunction in Pravastatin Treated Hypercholesterolemic Mice

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INTRODUCTION: Statins are medicines widely used in the treatment of familiar hypercholesterolemia because they inhibit the rate-limiting step of cholesterol biosynthesis. Hepatic enzymes abnormalities and mitochondrial dysfunction, such as higher susceptibility to mitochondria membrane permeability transition (MPT), were reported in statins users. **OBJECTIVES:** The aim of the present study was to clarify mechanisms underlying hepatotoxicity caused by pravastatin in hypercholesterolemic LDL receptor knockout mice ($LDLr^{-/-}$). Furthermore, the potential protective role of creatine supplementation, which protects against MPT and acts as an antioxidant, were also evaluated in this model. **MATERIAL AND METHODS:** MPT, measured as cyclosporine A sensitive mitochondrial calcium release (CaGreen-5N), mitochondrial oxidative stress (Amplex Red® and H_2DCF-DA) and antioxidant enzyme activities were evaluated in isolated liver mitochondria or liver homogenates from $LDLr^{-/-}$ mice treated with therapeutic doses of pravastatin (40 mg/kg/day, 90 days) and pravastatin plus creatine (last 15 days with diet containing 2% by weight). **RESULTS AND DISCUSSION:** We observed increased susceptibility to MPT and higher reactive oxygen content in pravastatin treated compared to control $LDLr^{-/-}$ mice (35%). Creatine supplementation significantly reduced both susceptibility to MPT and mitochondrial oxidative stress in pravastatin compared to control group. Pravastatin treatment caused no differences in superoxide dismutase, catalase, glutathione reductase and peroxidase activities. Interestingly, pravastatin increased by 30% the activity of glucose-6-phosphate dehydrogenase (G6PD), a key enzyme that supplies reducing equivalents as NADPH to cells. Creatine supplementation equaled G6PD activity in both control and pravastatin mice. **CONCLUSIONS:** Taken together, these results indicate that pravastatin induces liver Ca^{2+} mediated MPT and mitochondrial oxidative stress in $LDLr^{-/-}$ mice in a mechanism counteracted by creatine.

Keywords: Pravastatin, Liver toxicity, Mitochondria permeability transition (MPT).

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