Pravastatin Induced Mitochondrial Membrane Permeability Transition in Hypercholesterolemic Mice Muscle: Protection by Creatine or Coenzyme Q_{10}

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INTRODUCTION: Statins are efficient cholesterol-lowering medicines utilized worldwide. However, 10% of patients suffer from adverse effects and muscular symptoms. Pro- or antioxidant effects of statins have been a matter of debate. **OBJECTIVE:** Here we studied mitochondrial function and antioxidant enzymes activities in plantar muscle biopsies taken from control or pravastatin treated (40 mg/kg/day) LDL receptor knockout mice (*LDLr*$^{-/-}$) during 3 months. **MATERIAL AND METHODS:** Muscles with distinct metabolism and fiber type composition were harvested and evaluated for respiration rates and antioxidant enzymes activities. **RESULTS AND DISCUSSION:** The results showed normal rates of respiration induced by ADP, oligomycin or FCCP when the muscle biopsies were incubated in Ca^{2+} free medium. However, in the presence of 4 μM Ca^{2+}, these rates of respiration were inhibited up to 40% via mechanisms sensitive to EGTA, cyclosporin A, ruthenium red or coenzyme Q_{10} (CoQ_{10}) suggesting that pravastatin induces mitochondrial membrane permeability transition (MTP). Creatine, which exerts antioxidant effects and protection against MTP, when added to mice chow diet (2%), also protected against pravastatin plus Ca^{2+} harmful effects. Among several antioxidant enzymes, catalase activity was increased by 30% in plantar muscle of pravastatin treated mice. Taken together, these results suggest that the pravastatin treatment sensitizes plantar muscle mitochondria to Ca^{2+} dependent MPT via generation of a mild mitochondrial oxidative stress. This is strongly supported by protection conferred either by CoQ_{10} or creatine. **CONCLUSION:** Based on the concept of mitohormesis, we propose that a mild mitochondrial oxidative stress induced by pravastatin signals to a cell antioxidant response such as induction of catalase activity in *LDLr*$^{-/-}$ mice plantaris muscle and this explains the claimed antioxidant action of statins.

Keywords: familial hypercholesterolemia, pravastatin, skeletal muscle

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