CHRONIC PRAVASTATIN TREATMENT INDUCES Ca\(^{2+}\) MEDIATED MITOCHONDRIAL DYSFUNCTION AND INCREASED ANTIOXIDANT ACTIVITY IN SKELETAL MUSCLE OF \(L DLr^{-/-}\) MICE

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The safety and efficacy of statins treatment in hypercholesterolemic patients is well established. However, about 10% of patients develop side effects in skeletal muscle such as myalgia, myopathy and, rarely, rhabdomyolysis. Previous studies indicate that myotoxicity caused by statins may be linked to impairment of mitochondrial function associated with alterations in calcium homeostasis, inhibition of β-oxidation followed by oxidative stress. Thus, our aim is to evaluate mitochondrial function and antioxidant enzymes activities in LDL receptor knockout mice (\(L DLr^{-/-}\)), a model of familial hypercholesterolemia under 3 months of pravastatin treatment (40 mg/kg/day). Muscles with distinct metabolism and fiber type composition were harvested and evaluated for respiration rates and antioxidant enzymes activities. Our results show that pravastatin treatment slowed down the rates of ADP-, oligomycin- and FCCP-stimulated respiration (up to 40%) supported by glutamate/malate in permeabilized \(L DLr^{-/-}\) plantar muscle fiber bundles in the presence of Ca\(^{2+}\), compared to non-treated \(L DLr^{-/-}\). In contrast, no alterations were observed in soleus muscle. In addition, respiratory parameters were not altered in the presence of EGTA or cyclosporin A, a mitochondrial permeability transition inhibitor, indicating a possible Ca\(^{2+}\)-mediated respiratory impairment in plantaris muscle. Pravastatin treatment also increased catalase activity (48%) in plantaris muscle homogenates with no alterations in superoxide dismutase, glutathione reductase and peroxidase as well as glucose-6-phosphate dehydrogenase activities. No enzymatic alterations were observed in soleus muscle. Taken together our results indicate that different muscle fiber present distinct sensitivity to pravastatin as occur with other statins. Furthermore, Ca\(^{2+}\)-mediated mitochondrial dysfunction induced by pravastatin might act as a signal that leads to a higher activity of cellular antioxidant system in plantaris muscle of \(L DLr^{-/-}\) mice under this treatment.

**Keywords:** familial hypercholesterolemia, pravastatin, skeletal muscle

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