Effects of Simvastatin on mitochondrial respiration of rat skeletal muscle fibers

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3-Hydroxy-3-methylglutaryl CoA reductase inhibitors (statins) are safe and well-tolerated therapeutic drugs. However, they occasionally induce adverse effects, mainly myotoxicity and hepatotoxitity. Here, we investigated the effects of statin, *in vivo* and *in vitro*, on mitochondrial respiratory fuction in skeletal muscle biopsies. Incubation (1 hour) of permeabilized *soleus* muscle biopsies (2 mg) with crescent doses of simvastatin (1 to 40 μM) reduced the maximum ADP- or FCCP-stimulated mitochondrial respiration rate in a dose-dependent manner without changes in resting respiration rate (oligomycin-sensitive). The effects of a low simvastatin dose (1 μM) was prevented by coincubation with 1 mM L-carnitine, 100 μM mevalonate or 10 μM coenzyme Q10. The last two compounds are a product and an isoprenoid intermediary metabolite of HMG-CoA reductase, respectively. Cyclosporin A, an inhibitor of mitochondrial permeability transition, had no effect. *Soleus* muscle biopsies from rats treated during 15 days with therapeutic doses (100 mg/kg, p.o.) of simvastatin presented reduced oxygen consumption rates under all respiratory states while respiration of mitochondria isolated from this muscle presented no significant difference compared to mitochondria isolated from control rats. Altogether, these mitochondrial alterations may explain the myotoxicity observed in vivo and attributable to inhibition of HMG-CoA reductase, and reduction of ubiquinone pool into the electron transfer chain. Experiments are currently under way in order to characterize the mechanisms of L-carnitine protection against simvastatin-induced respiration inhibition.

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