Mitochondrial dysfunction in rat skeletal muscle fibers treated with simvastatin

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Statins (3-Hydroxy-3-methylglutaryl CoA reductase inhibitors) are safe and well-tolerated therapeutic drugs that occasionally induce myotoxicity such as myopathy and rhabdomyolysis. Here, we investigated the effects of simvastatin, on mitochondrial function in skeletal muscle bundles in vitro. One-hour incubation of permeabilized soleus muscle samples (~2 mg) with varying doses of simvastatin (1 to 40 µM) slowed the maximum ADP- or FCCP-stimulated mitochondrial respiration rates supported by glutamate/malate in a dose-dependent manner, but no changes in resting and oligomycin-inhibited respiration rates were observed. Simvastatin (1 µM) also reduced the maximum ADP-stimulated mitochondrial respiration supported by succinate but not by TMPD/ascorbate. This concentration of simvastatin also increased lactate release from soleus samples. Coincubation of samples with 1 mM L-carnitine, 100 µM mevalonate or 10 µM coenzyme Q10 abolished these simvastatin effects on mitochondrial glutamate/malate-supported respiration and on lactate release. Mevalonate and Q10 are products of the pathway sensitive to HMG-CoA reductase inhibition, while L-carnitine has many protective properties against myotoxicity. Simvastatin (1µM) led to coenzyme Q10 reduction (~44%) in soleus muscle, an event that was prevented by coincubation with mevalonate, but not with L-carnitine. Otherwise, simvastatin increased the production of hydrogen peroxide, an effect that was prevented by mevalonate, L-carnitine or Q10. Thus, independently of Coenzyme Q10 levels, L-carnitine can prevent the toxic effects of simvastatin. This indicates that mitochondrial respiratory dysfunction induced by simvastatin is not attributable to lower coenzyme Q10 pool in the electron transfer chain. Alternatively, all of these compounds protected against simvastatin induced hydrogen peroxide generation by mitochondria suggesting that this may be a common denominator mediating the myotoxicity.

Word Keys: Statin, Mitochondrial dysfunction, Skeletal muscle, Myotoxicity.

Supported by: CAPES, CNPq, FAPESP, FAEPEX-UNICAMP