Publication

PGC-1α plays a pivotal role in simvastatin-induced exercise impairment in mice

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Statins decrease cardiovascular complications, but can induce myopathy. Here, we explored the implication of PGC-1α in statin-associated myotoxicity.; We treated PGC-1α knockout (KO), PGC-1α overexpression (OE) and wild-type (WT) mice orally with 5 mg simvastatin kg; -1; day; -1; for 3 weeks and assessed muscle function and metabolism.; In WT and KO mice, but not in OE mice, simvastatin decreased grip strength, maximal running distance and vertical power assessed by ergometry. Post-exercise plasma lactate concentrations were higher in WT and KO compared to OE mice. In glycolytic gastrocnemius, simvastatin decreased mitochondrial respiration, increased mitochondrial ROS production and free radical leak in WT and KO, but not in OE mice. Simvastatin increased mRNA expression of Sod1 and Sod2 in glycolytic and oxidative gastrocnemius of WT, but decreased it in KO mice. OE mice had a higher mitochondrial DNA content in both gastrocnemius than WT or KO mice and simvastatin exhibited a trend to decrease the citrate synthase activity in white and red gastrocnemius in all treatment groups. Simvastatin showed a trend to decrease the mitochondrial volume fraction in both muscle types of all treatment groups. Mitochondria were smaller in WT and KO compared to OE mice and simvastatin further reduced the mitochondrial size in WT and KO mice, but not in OE mice.; Simvastatin impairs skeletal muscle function, muscle oxidative metabolism and mitochondrial morphology preferentially in WT and KO mice, whereas OE mice appear to be protected, suggesting a role of PGC-1α in preventing simvastatin-associated myotoxicity.
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