Susceptibility to simvastatin-induced toxicity is partly determined by mitochondrial respiration and phosphorylation state of Akt

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Statins are widely used to prevent cardiovascular diseases. They arewell-tolerated, with side-effects mainly seen in skeletal muscle. How theseside-effects are caused is unknown. We compared isolated primary mouse skeletalmuscle myocytes, C2C12 myotubes and liver HepG2 cells to detect differences that could uncover why statins are toxic in skeletal muscle but less so in the liver. 10μM simvastatin caused a decrease in mitochondrial respiration in the primarymouse myocytes and C2C12 myotubes, but had no effect in the HepG2 cells.Mitochondrial integrity is maintained by multiple signaling pathways. One ofthese pathways, Igf-1/Akt signaling, is also heavily implicated in causingstatin-induced toxicity by upregulating atrogin-1. We found that phosphorylatedAkt was reduced in C2C12 myotubes but not in HepG2 cells. HepG2 mitochondrialrespiration became susceptible to simvastatin-treatment after Akt inhibition, andmitochondrial respiration was rescued in Igf-1-treated C2C12 myotubes. Theseresults suggest that disruption of Igf-1/Akt signaling is a causative factor insimvastatin-induced mitochondrial dysfunction in C2C12 myotubes, whereas HepG2cells are protected by maintaining Igf-1/Akt signaling. We conclude thatphosphorylation of Akt is a key indicator of susceptibility to statin-inducedtoxicity. How statins can disrupt Igf-1/Akt signaling is unknown. Statins reduce geranylgeranylation of small GTPases, such as Rap1. Previous studies implicateRap1 as a link between cAMP/Epac and Igf-1/Akt signaling. Transient transfection of constitutively active Rap1 into C2C12 myotubes led to a partial rescue ofsimvastatin-induced inhibition of mitochondrial respiration, providing a novellink between signaling and respiration.

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