IGF-1 prevents simvastatin-induced myotoxicity in C2C12 myotubes

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Statins are generally well tolerated, but treatment with these drugs may be associated with myopathy. The mechanisms of statin-associated myopathy are not completely understood. Statins inhibit AKT phosphorylation by an unclear mechanism, whereas insulin-like growth factor (IGF-1) activates the IGF-1/AKT signaling pathway and promotes muscle growth. The aims of the study were to investigate mechanisms of impaired AKT phosphorylation by simvastatin and to assess effects of IGF-1 on simvastatin-induced myotoxicity in C2C12 myotubes. C2C12 mouse myotubes were exposed to 10ăμM simvastatin and/or 10ăng/mL IGF-1 for 18ăh. Simvastatin inhibited the IGF-1/AKT signaling pathway, resulting in increased breakdown of myofibrillar proteins, impaired protein synthesis and increased apoptosis. Simvastatin inhibited AKT S473 phosphorylation, indicating reduced activity of mTORC2. In addition, simvastatin impaired stimulation of AKT T308 phosphorylation by IGF-1, indicating reduced activation of the IGF-1R/PI3K pathway by IGF-1. Nevertheless, simvastatin-induced myotoxicity could be at least partially prevented by IGF-1. The protective effects of IGF-1 were mediated by activation of the IGF-1R/AKT signaling cascade. Treatment with IGF-1 also suppressed muscle atrophy markers, restored protein synthesis and inhibited apoptosis. These results were confirmed by normalization of myotube morphology and protein content of C2C12 cells exposed to simvastatin and treated with IGF-1. In conclusion, impaired activity of AKT can be explained by reduced function of mTORC2 and of the IGF-1R/PI3K pathway. IGF-1 can prevent simvastatin-associated cytotoxicity and metabolic effects on C2C12 cells. The study gives insight into mechanisms of simvastatin-associated myotoxicity and provides potential targets for therapeutic intervention.
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