Role of PGC-1-alpha-associated Mitochondrial Biogenesis in Statin-induced Myotoxicity

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Aim: Statins are well tolerated but can be associated with mitochondrial dysfunction in skeletal muscles. Statins impair mitochondrial proliferation by decreasing PGC-1α expression in human and rat skeletal muscle, suggesting a role of PGC-1α in statin-induced myotoxicity. This study aimed to investigate these effects in differentially expressed PGC-1α mouse models.

Methods: We used three mouse models: mice with muscle PGC-1α knockout (MKO), mice overexpressing PGC-1α (MCK), and wild-type (WT) mice. Mice were treated for 3 weeks with water or simvastatin (5 mg/kg/d) by oral gavage. We determined exercise capacity, muscle function and the function of muscle mitochondria from glycolytic gastrocnemius and soleus oxidative muscles.

Results: Simvastatin showed muscular impairments in WT mice, manifested by decreased exercise capacity, grip strength and mitochondrial respiration in the glycolytic muscle, coupled with increased H_2O_2 production. Moreover, MKO mice treated with simvastatin exacerbated these muscular dysfunctions and showed impaired mitochondrial respiration in oxidative and glycolytic muscle types. However, MCK mice showed no impairments in exercise capacity and muscle function.

Conclusion: Increased muscle PGC-1α expression ameliorated statin-induced muscular dysfunctions, while decreased muscle PGC-1α expression further exacerbated the toxicity. Therefore, PGC-1α seems to be a susceptibility factor and has an important role in mitigating simvastatin-induced myotoxicity. ■