Nitric Oxide Mitigates Atorvastatin-Induced Muscle Dysfunction And Alterations in Mice

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Statin-related myopathy is an important cause of statin intolerance and discontinuation of treatment. It is recognized that nitric oxide (NO) has a key role in regulating muscle function, such as myocyte differentiation, mitochondrial biogenesis and regulation of blood flow in the exercising muscle. Herein, we have compared the effects of NCX 6560, a dual acting molecule combining atorvastatin activity and NO donation, with atorvastatin on skeletal muscle function and structure in C57/Bl6 mice.

Mice (n=15/group 4 months of age) were treated with either atorvastatin (40 mg/kg/day) or an equimolar dose of NCX 6560 (48 mg/kg/day) for 2 months. Incorporation of the drug into the diet led to similar plasma levels of atorvastatin and its active metabolites (2-OH-atorva and 4-OH-atorva). Skeletal muscle function was evaluated in vivo by exhaustion treadmill test (at 10, 30, 45 and 60 days), and ex vivo by measuring absolute (Po) and specific (Po/CSA) tension in isolated tibialis muscle preparations. Citrate synthase activity (CS) was measured as a marker of mitochondrial function in the gastrocnemius, diaphragm and heart.

After 10 days, the mice treated with atorvastatin showed a large deterioration of time to exhaustion which was stable until the end of treatment (p<0.001 vs vehicle at all time points), whereas those treated with NCX 6560 maintained a fully preserved in vivo muscle function (p<0.05 vs atorva at all time points). Atorvastatin caused a significant reduction of Po (12±5 vs 23±9 g vehicle, p<0.05) and Po/CSA (0.17±0.05 vs 0.3±0.05 g/µL vehicle, p<0.05) in the tibialis muscle, whereas NCX 6560 preserved muscle functional activity (Po: 25±11 g; Po/CSA: 0.33±0.15 g/µL).

The muscle dysfunction induced by atorvastatin was associated with a 6-fold increase of serum creatine kinase (CK) (322±92 vs 82±21 U/L vehicle, p<0.001) and Evans blue positive fibers in the tibialis and diaphragm. Moreover, atorvastatin induced muscle fiber atrophy in both the tibialis (1724±739 vs vehicle: 2182±666 µm²) and gastrocnemius (1645±486 vs 1871±440 µm² vehicle). On the contrary, NCX 6560 prevented serum CK increase (175±51 U/L) and did not induce fiber atrophy (tibialis: 2197±665, gastrocnemius: 2288±743 µm²), thus preserving muscle structure. Finally, atorvastatin induced a significant reduction of CS in the gastrocnemius (14±3 vs 35±6 mmol/min/mg vehicle, p<0.001) diaphragm (40±4 vs 48±5 vehicle, p<0.05) and the heart (43±2 vs 56±7 vehicle, p<0.05), suggesting an impairment of mitochondrial function. Conversely, NCX 6560 prevented a CS decrease partly in the gastrocnemius (28±2) and completely in the diaphragm (54±2) and heart (51±2).

This study shows that a 2-month treatment with atorvastatin induces deterioration of muscle function, accompanied by an increase of serum CK, muscle fiber atrophy and a compromised CS activity, whereas NCX 6560 does not induce deleterious effects on muscle function and structure. In conclusion, these data suggest a significant prevention of statin myopathy by NO donation and thus, this investigational NCX 6560 could represent a safe alternative to those patients who are unable to tolerate statin therapy.