TACSM Abstract

Mediation of the Translocation of nNOSμ During Unloading-Induced Atrophy of Skeletal Muscle via NOX2 Inhibition

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ABSTRACT

Mechanical unloading results in detachment of the mu-splice variant of neuronal nitric oxidase synthase (nNOSμ) from the dystrophin-glycoprotein complex and sarcolemma and translocation to the cytosol. We recently found that reactive oxygen species (ROS) play a role in nNOSμ translocation during unloading and muscle atrophy. NOX2, an isoform of NADPH oxidase and source of ROS, may play a causal role in nNOSμ translocation. The purpose of the study was to determine the effectiveness of NOX2 peptidyl inhibition in reducing the translocation of nNOSμ from the sarcolemma and subsequently soleus CSA. Adult male Fisher 344 rats were randomly assigned to one of three groups: CON (control), HU-S (hind limb unloaded with gp91ds-tat scramble) and HU-G (hind limb unloaded with gp91ds-tat). The hind limb unloading period was 7 days. Mean body weights for CON (353.26 g ± 15.47), HU-S (305.14 g ± 18.18) and HU-G (306.34 g ± 16.84) at the beginning of the experiment were not significantly different. Muscle mass/body mass ratio for the gastrocnemius complex (gastrocnemius, plantaris and soleus) was significantly reduced in HU-S rats (10.08 mg/g ± 0.24) but was maintained in HU-G rats (10.88 mg/g ± 0.47). SMASH analysis revealed that average soleus CSA in HU-G rats (3293.08 μm^2 ± 46.82) decreased significantly less than HU-S rats (2606.66 μm^2 ± 33.46) compared with ambulatory controls ($p > 0.0001$). Immunofluorescence and staining of nNOS activity with NADPH Diaphorase of soleus tissue showed considerable loss of sarcolemmal nNOSμ in the HU-S group while the HU-G group revealed substantial maintenance of nNOSμ at the sarcolemma. The results of this study suggest that NOX2 inhibition via gp91ds-tat is effective in reducing the translocation of nNOSμ from the sarcolemma to the cytosol and maintaining CSA of the soleus with mechanical unloading via the inhibition of NOX2.