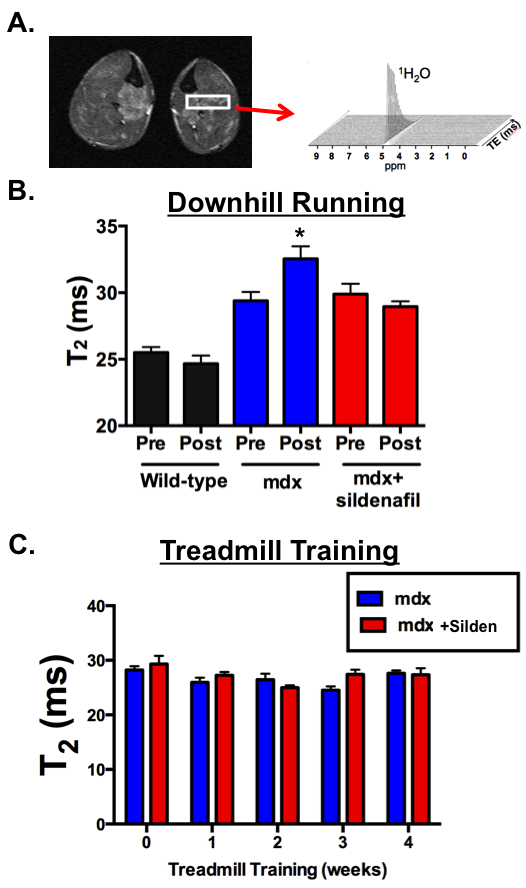
**Effects of PDE5A Inhibition on Skeletal Muscle 1H2O T2 after Exercise in Dystrophic Mice**

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**Introduction**

Dystrophic muscle is characterized by increased susceptibility to muscle damage, inflammation, reduced blood flow, and fatigue. These impairments may be enhanced by lack of sarcolemma-localized neuronal nitric oxide synthase (nNOS) (1, 2). In this study, we examined whether a phosphodiesterase 5 inhibitor (sildenafil citrate) would reduce muscle damage and improve exercise performance in *mdx* mice after downhill running and during a low-intensity treadmill training program. Single voxel 1H-MRS measures of muscle T2 were utilized as an indicator of muscle damage(3).



**Figure 1.** 1H-MRS relaxometry derived 1H2O T2 values from the medial compartment of the hindlimb (1A.) after downhill running (1B) and during four weeks of endurance training in *mdx* with and without treatment of sildenafil (C).

**Experimental**

Dystrophic (*mdx*) and wild-type mice performed a downhill running protocol (6-12m/min; 30-60min;14o decline) and low-intensity progressive treadmill training five days a week over a four week period (8-12m/min; 25-60min;0o incline). Training was performed in *mdx* mice with (n=5) and without (n=10) administration of sildenafil citrate (400 mg/L drinking water, *ad libitum*) and in wild-type (n=5) mice (age 9-17 months). 1H-MRS single voxel STEAM (10-128 TE’s, 5-300 ms, TR 9 s) was used to acquire data from the medial compartment (MC) of the lower hindlimbs 24 hours after downhill running and at weekly intervals during the training program using a 4.7T Varian/Agilent MR operating system of the Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) facility (Fig. 1A).

**Results and Discussion**

Sildenafil citrate diminished the increase in T2 of skeletal muscles 24 hours after downhill running in *mdx* mice, suggesting reduced muscle damage (Fig. 1B). During training, the prescribed distance completed was greater in treated *mdx* mice (98%) and controls (100%) than untreated *mdx* mice (60%). At baseline, 1H2O T2 was greater (p<0.05) in the *mdx* for all groups (28.7±1.6ms) compared to control (22.8±1.6ms) mice. T2 values were maintained in controls and *mdx* mice throughout training and were not elevated after four weeks of running compared to baseline (Fig. 1C).

**Conclusions**

Our findings indicate that treatment with sildenafil reduced muscle damage from downhill running in *mdx* mice. Furthermore, the progressive low-intensity treadmill training program did not lead to additional muscle damage/ inflammation in *mdx* mice. In addition, the effects of training were enhanced by sildenafil, as evident by improved performance during training of the treated mice.

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