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

Batra, A. (UF, Physical Therapy); Vohra, R.; Chrzanowski, S. (UF, Physiology and Functional Genomics); Lott, D. (UF, Physical Therapy); Walter, G.A. (UF, Physiology and Functional Genomics); Vandenborne, K. (UF, Physical Therapy) and Forbes, S.C. (UF, Physical Therapy)

**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.

**Acknowledgements**

 This research was supported by the Muscular Dystrophy Association (175552). A portion of this work was performed at the National High Magnetic Field Laboratory, which is supported by National Science Foundation Cooperative Agreement No. DMR-1157490, the State of Florida, and the U.S. Department of Energy.

**References**

1. Tidball & Wehling-Henricks. J Physiol. 592(Pt 21):4627-38, 2014.

2. Kobayashi et al. Nature. 27(456(7221)):511-5, 2008.

3. Mathur et al. Muscle Nerve. 43(6):878-86, 2011.