**Effects of PDE5A inhibition on skeletal muscle T2**

**after low intensity treadmill training 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 phosophodiesterase 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. MRI T2 was utilized as an indicator of muscle damage(3).

**Experimental**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Week 1 | Week 2 | Week 3 | Week 4 |
| Tibialis Anterior (TA) | Wild ctrl | 24.5±2.1 | 22.8±2.5 | 23.3±2.2 | 23.1±1.6 |
| *mdx*train | 26.3±4.1 | 25.5±2.7 | 24.7±2.2 | 25.1±1.7 |
| *mdx*sil&train | 26.1±2.3 | 25.6±1.8 | 25.6±2.6 | 25.8±3.3 |
| Medial Compartment (MC) | Wild ctrl | 24.3±2.1 | 24.1±3.5 | 23.7±2.0 | 24.2±2.6 |
| *mdx*train | 26.1±1.8 | 25.2±1.9 | 25.3±1.6 | 26.3±2.0 |
| *mdx*sil&train | 27.6±2.2 | 25.3±1.5 | 25.7±1.6 | 26.1±2.1 |
| Gastrocnemius (GAS) | Wild ctrl | 24.3±1.2 | 23.8±1.5 | 23.5±1.3 | 24.3±1.0 |
| *mdx*train | 26.4±1.7 | 24.9±1.2 | 25.5±1.3 | 26.0±1.5 |
| *mdx*sil&train | 26.9±1.8 | 25.6±1.0 | 25.1±1.0 | 25.1±1.3 |

Dystrophic (*mdx*) and wild-type mice performed a low-intensity progressive treadmill training five days a week over a four-week period (8-12m/min; 25-60min;0o incline). Mice treated with sildenafil citrate (mdxsil: n=5) were compared to untreated mice (mdx: n=5; wild-type: n=5). To evaluate muscle damage, magnetic resonance imaging (MRI) transverse relaxation time constant (T2) of muscles in the lower hind limbs was calculated. A custom built 200 MHz 1H solenoid coil with 2 cm internal diameter was used to image hindlimbs. Proton T2 weighted multi slice spin echo images were acquired (TR: 2000 ms, TE:14 and 40 ms, FOV: 15X15mm, slice thickness:0.5mm acquisition matrix: 128 x 256) using a 4.7T Agilent/Varian MR system.

Table 1: MRI T2 of hindlimb compartments following downhill running. B. Hindlimb T2 during 4 weeks of low intensity training.

**Results and Discussion**

 Muscle T2 values were maintained in controls and *mdx* mice throughout training and were not elevated after four weeks of running compared to baseline (Table 1). During training, the prescribed distance completed was greater in treated *mdx* mice (98%) and controls (100%) than untreated *mdx* mice (60%) (Fig 1).

**Conclusions**

Our findings indicate that 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.

Fig 1: Percentage of total distance covered by different groups during training

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**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.