



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 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. MRI T₂ was utilized as an indicator of muscle damage(3).

Experimental

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; 0° incline). Mice treated with sildenafil citrate (*mdx^{sil}*; 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.

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.

Acknowledgements

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References

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

		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
	<i>mdx^{train}</i>	26.3±4.1	25.5±2.7	24.7±2.2	25.1±1.7
	<i>mdx^{sil&train}</i>	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
	<i>mdx^{train}</i>	26.1±1.8	25.2±1.9	25.3±1.6	26.3±2.0
	<i>mdx^{sil&train}</i>	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
	<i>mdx^{train}</i>	26.4±1.7	24.9±1.2	25.5±1.3	26.0±1.5
	<i>mdx^{sil&train}</i>	26.9±1.8	25.6±1.0	25.1±1.0	25.1±1.3

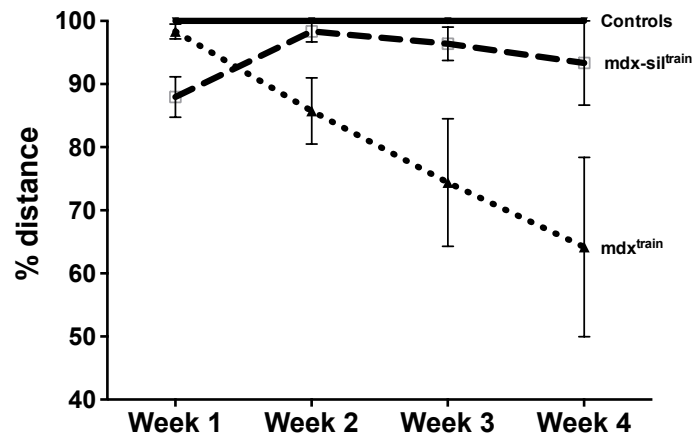


Fig 1: Percentage of total distance covered by different groups during training