Effects of downhill running on skeletal muscle of dystrophic mice evaluated by MR T_2 and ^{31}Phosphorus-magnetic resonance spectroscopy

Lopez, C.J., Moslemi, Z., Batra, A., Rennick, A. (UF, Department of Physical Therapy), Walter, G.A.(UF, Department of Physiology), Zeng, H. (UF, AMRIS), Forbes, S.C. (UF, Department of Physical Therapy)

Introduction

In this study we examined the effects of downhill treadmill running on dystrophin-deficient skeletal muscle of young *mdx* mice, an animal model of Duchenne muscular dystrophy (DMD). We hypothesized that young *mdx* mice would be susceptible to muscle damage following downhill running and this would be associated with increased muscle T_2, altered muscle energetic status, and intracellular magnesium (Mg^{2+}).

Experimental

Mice (wild-type 5, *mdx* 5) underwent downhill running (14^{O} decline) on a motorized treadmill at a speed of 8-10 m/min, for 45-60 min [1]. MR T_2 and unlocalized ^{31}phosphorus magnetic resonance spectroscopy (^{31}P-MRS) data were collected using a 4.7T and 11.1T MR systems of the Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) facility of the NHMFL. T_2-weighted, multiple-slice, single spin-echo MR axial images were acquired (TR 2s, TE 14/40 ms, 12 slices) from the hindlimbs. MRI T_2 values were calculated on a pixel-by-pixel basis for the anterior compartment (AC), posterior compartment (PC), and the deep medial region between the tibia and fibula (MC). In addition, single voxel ^{1}H-MRS data were acquired from the soleus and gastrocnemius using stimulated echo acquisition mode (STEAM; TR 9 s, 16 TE's exponentially spaced: 5-288 ms, 4 phase cycles). Finally, data were acquired from the posterior hindlimb compartment to measure adenosine triphosphate (ATP), phosphocreatine (PCr), inorganic phosphates (Pi), intracellular pH, and magnesium (Mg^{2+}) before and 24 hours after exercise.

Results and Discussion

In wild-type, there were no increases in muscle T_2 observed after downhill running. However, in *mdx* mice, a composite measure of muscle T_2 from all muscle groups showed a significant increase after downhill running compared to before downhill running (Fig. 1). Also, downhill running resulted in a significant ($p<0.01$) decrease in relative intracellular Mg^{2+} concentration in *mdx* compared to pre-exercise (Pre: $\bar{x} = 398 \pm 72\ \mu M$; post: $\bar{x} = 241 \pm 50\ \mu M$) but no differences were observed in wild-type. Furthermore, there was a trend ($p=0.18$) towards an elevated Pi/PCr in the gastrocnemius and soleus muscles in *mdx* after exercise compared to before exercise (Pre: $\bar{x} = 0.046 \pm 0.028$; post: $\bar{x} = 0.061 \pm 0.018$). The energetic alterations in *mdx* were enhanced in the regions of muscle damage identified with T_2-weighted MRI.

Conclusions

Our findings support that acute muscle damage induced by downhill running can be detected in young dystrophic mice using quantitative MR T_2. Also, downhill running resulted in intracellular changes in *mdx* mice evident with ^{31}P-MRS, including lower intracellular Mg^{2+} concentrations, likely due to compromised sarcolemma integrity. Overall, MR T_2 and ^{31}P-MRS measures are sensitive to acute muscle damage induced by downhill running and may be a valuable techniques for testing potential therapeutic interventions in dystrophic muscle.

Acknowledgements

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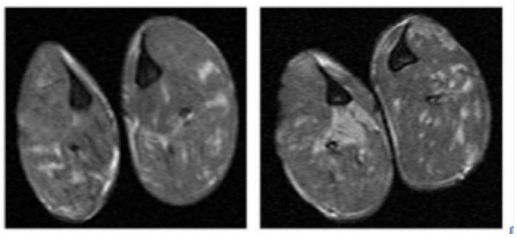

Fig.1 Example T_2-weighted transaxial images of an *mdx* mouse prior to (left) and following (right) downhill running.

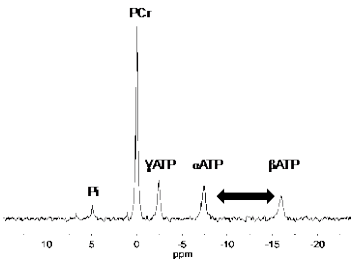

Fig. 2 Example phosphorous spectrum of a control mouse hindlimb acquired at 11.1T after downhill running. Mg^{2+} is estimated from the chemical shift difference between αATP and βATP (double headed black arrow).

References

[1] Mathur, S., *et al*., Muscle & Nerve, **43**(6), 878-886 (2011).