

Effects of Treadmill Exercise on Muscle Fibers in Mice with Steroid Myopathy

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Abstract. We studied the effect of treadmill exercise on muscle fibers in mice with experimental steroid myopathy. Frozen sections of the extensor digitorum longus (EDL) and soleus (SOL) muscles were stained with hematoxylin-eosin, and the muscle fiber diameters measured. In the EDL, muscle fiber diameters in the steroid groups decreased significantly compared with those in the control groups; moreover, muscle fiber diameters in the exercise groups increased significantly compared with those in the non-exercise groups, whereas the diameters in the SOL did not differ. We speculate that treadmill exercise may prevent corticosteroid-induced muscle fiber atrophy.

Key words: steroid myopathy, muscle fiber, exercise

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Corticosteroid therapy is a common clinical treatment for autoimmune diseases such as multiple sclerosis, myasthenia gravis, and rheumatoid arthritis, and steroid myopathy is a common side-effect of systematically administered corticosteroids¹⁻⁴. It is not clear, however, whether therapeutic exercises can prevent corticosteroid-induced muscle atrophy during corticosteroid therapy. We therefore examined the effect of treadmill exercise on the muscle fibers of mice with experimental steroid myopathy.

Materials and Methods

We used 20 male C57BL/10ScSn mice, aged 32 weeks, randomly divided into four groups: control non-exercise (CN), control exercise (CE), non-exercise with steroid (SN), and exercise with steroid (SE). In the steroid groups, a 2 mg/kg dose of dexamethasone sodium phosphate was injected to the upper lumbar region subcutaneously 6 days/week for 5 weeks. The control groups likewise were

injected with 2 ml/kg normal saline solution 6 days/week for 5 weeks. During the experimental period, the mice were able to move in the cage, to drink water and eat food freely. The mice with exercise were forced to run on a treadmill (Model-SN460 Sinano Ltd., Tokyo) at 10 m/min^{5,6} for 20 min/day, 6 days/week for 5 weeks. At the end of the experimental period, the extensor digitorum longus (EDL) and soleus (SOL) muscles were extracted. Frozen sections of these muscles were stained with hematoxylin-eosin. The experimental protocol used was approved by the Ethics Review Committee for Animal Experimentation at our institution⁷.

The diameters of 200 muscle fibers from each of the muscles were measured with a personal computer and the public domain NIH Image program. Results were analyzed by a two-way analysis of variance (two-way ANOVA). If the interaction was showed ($p < 0.05$), pairwise comparisons were made using non paired Student's t-test.

Results

In the EDL, muscle fiber diameters in the steroid groups decreased significantly ($p < 0.01$) compared with those in the control groups, the means of the muscle fiber

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diameters in the exercise groups increased significantly ($p < 0.01$) compared with those in the non-exercise groups. There was not the interaction between steroid and exercise (Fig. 1a).

In the SOL, muscle fiber diameters in the steroid groups decreased significantly ($p < 0.01$) compared with those in the control groups, and the means of the muscle fiber diameters in the exercise groups did not showed significant difference from those in the non-exercise groups. There was the interaction between steroid and exercises ($p < 0.01$). However, result from non paired Student's t-test, muscle fiber diameters in the group CN did not showed significant difference from those in the group SN (Fig. 1b). These statistical data induced that there was not significance in the difference of the mean fiber diameters between the steroid groups and the control groups in the SOL.

No necrotic fibers was found in this experiment.

Discussion

Our data show that corticosteroid administration induced muscle fiber atrophy in the EDL but not in the SOL. Furthermore, the muscle fibers showed no atrophy

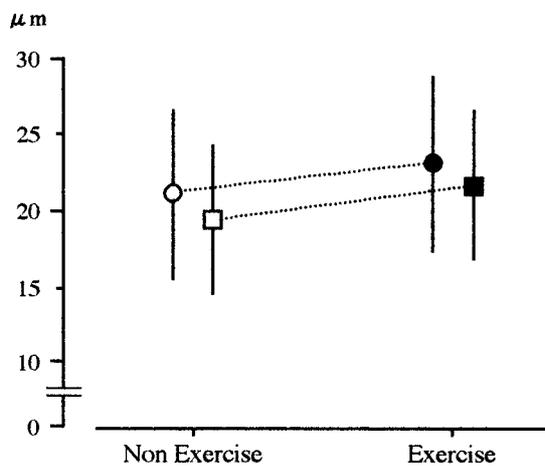
during treadmill exercise in spite of corticosteroid being administered in the EDL.

The EDL is composed mainly of type II fibers, and the SOL of type I fibers. ATP is produced by fatty acid oxidation in type I fibers, but it is not produced in type II fibers. Corticosteroids also inhibit the synthesis of muscle protein and ATP^(8,9), thereby inducing accelerated protein degradation and muscle fiber atrophy in the EDL.

There are a few reports that physical training restores atrophied muscle in corticosteroid-treated humans and animals. Horber *et al.* showed that in humans isokinetic training of knee extension-flexion increased the thigh femoral muscle area, decreased the thigh fat area, and normalized the mean peak torque and total work output in 12 patients treated with prednisone⁽¹⁰⁾. Gardiner *et al.* reported that in rats isometric exercise, such as mild weight-lifting exercise, decreases atrophy of fast-twitch muscle fibers under chronic glucocorticoid administration⁽¹¹⁾. Takahashi reported that in rats free running exercise improve glucocorticoid-induced type II fiber atrophy⁽¹²⁾.

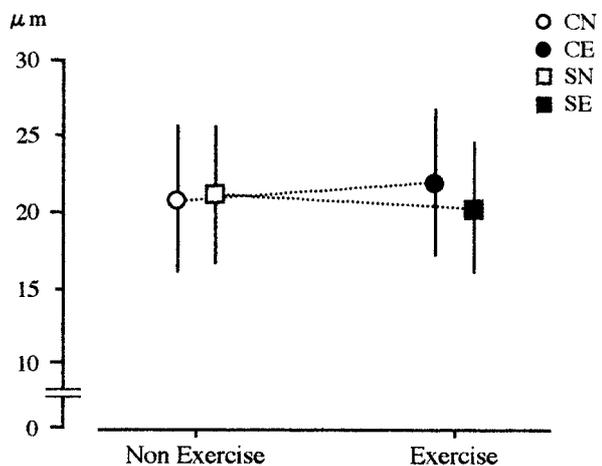
Physiological muscle overload, as in isometric and isokinetic exercise, results in hypertrophy of fast-twitch fibers in animals^(13,14) and humans⁽¹⁵⁻¹⁷⁾. The treadmill exercise, used as isotonic exercise, raises myofibrillar

a. EDL



Two-way ANOVA
Factor 1 (Control vs Steroid); $p < 0.01$
Factor 2 (Non Exercise vs Exercise); $p < 0.01$
Interaction (Factor 1 \times Factor 2); $p > 0.05$

b. SOL



Two-way ANOVA
Factor 1 (Control vs Steroid); $p < 0.01$
Factor 2 (Non Exercise vs Exercise); $p > 0.05$
Interaction (Factor 1 \times Factor 2); $p < 0.01$
Non paired student's t-test
CN vs SN; $p > 0.05$

Fig. 1 Means of muscle fiber diameters in the four groups.

In the extensor digitorum longus (EDL) muscle, the steroid groups decreased significantly ($p < 0.01$) compared with the control groups, and the exercise groups increased significantly ($p < 0.01$) compared with the non-exercise groups.

In the soleus (SOL) muscle, the steroid groups decreased significantly ($p < 0.01$) compared with the control groups, the exercise groups did not show significant difference from the non-exercise groups. There was the interaction between steroid and exercise statistically. Result from non paired Student's t-test of the group CN did not show significant difference from the group SN.

ATPase activity¹⁸⁾, and glycolytic or oxidative enzyme activities in normal rat skeletal muscles¹⁹⁾. These changes produced by treadmill exercise may prevent the muscle atrophy that reflects the corticosteroid-induced decrease of protein synthesis and ATP synthesis. And Takahashi had presumed that the running exercises inhibit the protein degradation and accelerate protein synthesis in type II fiber with steroid myopathy¹²⁾. However, the mechanism by which training exercise prevents corticosteroid-induced muscle atrophy is not known.

It is better for patients with steroid myopathy to have the dose of corticosteroid decreased, but it sometimes is impossible to do this because of the high activity of autoimmune diseases. This study showed that treadmill exercise was effective in preventing muscle atrophy in mice with experimental steroid myopathy. In humans, isotonic exercise may also prevent corticosteroid-induced muscle atrophy.

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