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Preventive effect of passive range of motion exercise on denervation-induced muscle atrophy

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KEY WORDS

prevention, passive range of motion exercise, denervation, muscle, atrophy

Following denervation induced by nerve transection or nerve damage, various changes occur in muscles. For example, the muscle fibers become highly sensitive to acetylcholine over their entire length instead of only at the end plate due to the extra-junctional spread of acetylcholine receptors[1]. The organelles contained in the muscle fibers undergo alterations[2], decreasing the mitochondrial oxidative capacity of the muscle fibers[3], with the neuromuscular junctions begining to degenerate[4], and, finally the fibers becoming atrophic[2].

Passive range of motion exercise (PRME) is often used as a therapeutic modality to delay the development of contracture, decrease fibrosis, as well as enhancing blood flow to the muscle[5]. Although PRME is extensively used in physical therapy practice, there is a dearth of studies that have evaluated its benefit.

In a study evaluating PRME on denervated limb muscle of laboratory animals, Petajan et al[6] reported no statistically significant difference in the mean fiber diameter between denervated-untreated and denervated-exercised muscles. The authors acknowledged that the PRME they employed imposed a mechanical strain on the denervated muscle fibers which resulted in many structural alterations of the muscle fibers as well as endomysial fibrosis. It would appear that such a mechanical strain might also induce additional necrosis and muscle atrophy. In view of this uncertainty, a study was carried out to investigate the effect of PRME on a rat muscle denervated by cutting the sciatic nerve and evaluate its effects on the muscle fibers.

MATERIAL AND METHOD

Fifteen male Wister rats (nine to twelve weeks of age) were used in this study. The ten animals were anesthetized with pentobarbital sodium (35mg/kg-body weight, ip). The right hind limb of these animals was denervated by excision of a 0.5-cm segment of the sciatic nerve just proximal to the bifurcation of the tibial and peroneal nerves. The cut end of the proximal portion of the nerve was capped with Silastic tube to prevent reinnervation. The Kanazawa University Ethics Committee approved the operation and experimental treatment for the Use and Care of Animals. The denervated animals were divided into two groups according to the treatment received. One group of five rats received PRME treatment, but the other group of five rats was untreated and served as denervated controls. The remaining five animals were not denervated nor exercised, serving as normal controls. PRME treatment commenced 24 h after surgery. Each rat was confined in a restrainer cage with its denervated foot secured with tape to a device designed to immobilize the ankle but allow flexion of the toes. A cut-away "boot" to support the ankle with

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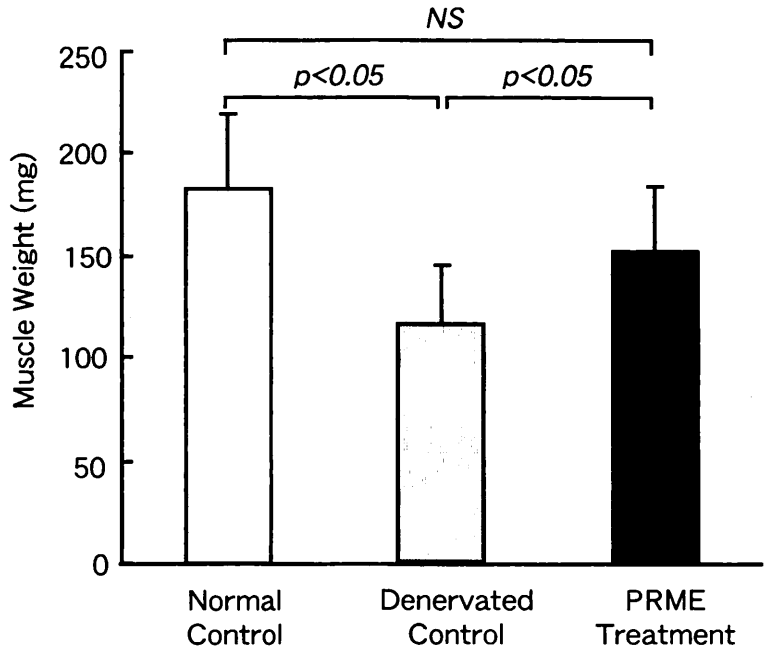

Figure 1. Mean muscle weight of the extensor digitorum longus muscle. Vertical line on top of the bar refers to standard deviation. Abbreviations : PRME, passive range of motion exercise ; NS , non-significant

a hinged "sole" to permit toe flexion and extension accomplished this. The hinge was forced up (toes extended) by a camshaft coupled to a small DC motor and forced down (toes flexed) by a spring attached to the underside of the hinge through the range of motion. The extensor digitorum longus (EDL) muscle was stretched, 10 times per minute, 30 minutes per day per rat for a total of 14 days. After 14 days of PRME treatment, the EDL muscles from the two denervated groups were exposed and the proximal end of the sciatic nerve was stimulated to ascertain if any reinnervation had occurred. No response was observed in any of the experimental animals. The EDL muscles from all groups were then removed, weighed, and frozen in isopentane cooled with liquid nitrogen quickly. Cross sections (10 μm) from the muscle belly were cut in a cryostat at -25℃. To differentiate muscle fiber types, the histochemical method for myofibrillar ATPase in the modification of Dubowitz[7] was used, and types I and II identified. To quantitate the degree of change in fiber size, an electronic graphics digitizer (Cosmozone 98, Nikon, Tokyo) was used to measure cross sectional areas of 100 muscle fibers per muscle from photomicrographs of ATPase-stained sections. The significance between the groups was determined by Student's t test. All p values below 0.05 were considered significant.

RESULTS

Muscle weight. Compared with normal control rats, the mean EDL muscle weight was 41, 19% smaller in denervated control, PRME treatment rats respectively (Fig. 1). There was a significant difference in EDL muscle weight between denervated control and PRME treatment rats. PRME was attenuated the loss in EDL muscle weight so that the mean muscle weight of PRME treatment rat was similar to that in the controls.

Fiber cross sectional area. The results of fiber sizes are summarized in Figure 2. It is apparent from Figure 2 that there was no significant difference for each experimental group as regards to the type I fiber's cross sectional area 14 days post-denervation. The type II fibers of both denervated groups atrophied compared with these of the normal control group. However, the type II fibers of the PRME treatment group were significantly larger ($p < 0.05$) than those of the denervated-control group.

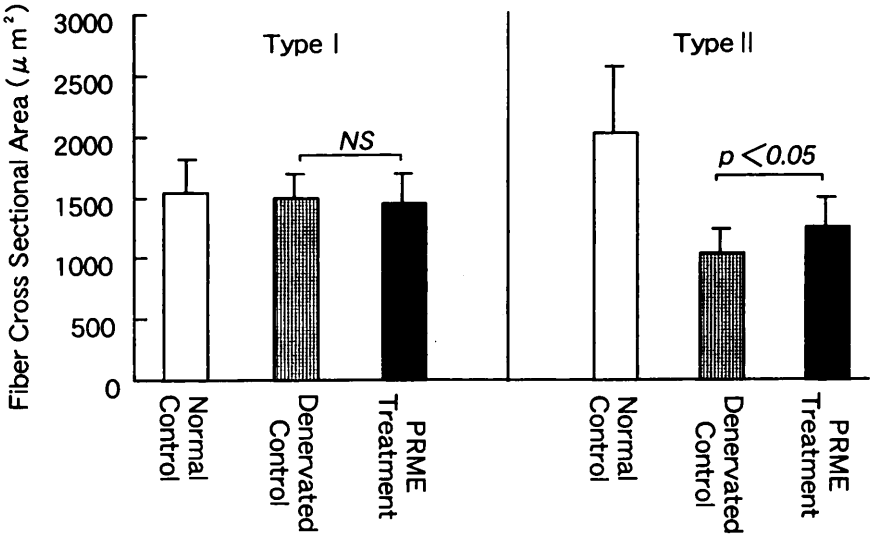

Figure 2. Type I and type II fibers of the rats' extensor digitorum longus muscles in normal control, denervated control, and PRME groups. Abbreviations : PRME, passive range of motion exercise ; NS, non-significant

DISCUSSION

Petajan et al[6] reported no statistically significant benefit for rabbit muscles that received passive exercise compared with nontreated denervated muscles after 3 weeks of treatment. In contrast, our data show that PRME is highly beneficial in retarding denervation atrophy in the type II muscle fibers. This is the predominant fiber population in rat EDL muscle.

The type I muscle fibers, as seen in the present study, were unaffected by denervation, at least within 14 days post-surgery. This is consistent with the findings of Niederle et al[8]. It has been suggested that the pronounced resistance of type I fibers to denervation atrophy may be due to their minor degree of neurotrophic dependence[9].

PRME has been shown to reduce joint contracture and edema as well as enhance circulation. The possibility exists that PRME might slow protein degradation in the muscle, thereby retarding the process of atrophy. Muscle activity is known to stimulate protein synthesis and inhibit protein breakdown[10]. Passive stretch was reported to inhibit protein breakdown in innervated muscle and was shown by Goldspink[11] to cause an increased accumulation of proteins and promote muscle growth in denervated muscle. Our data demonstrate that PRME in muscle without an intact nerve supply can retard muscle fiber atrophy at least to 14 days post-denervation. Presumably, it does so by inhibiting protein degradation.

Conclusion, a 14-day PRME produced a retardation of type II muscle fiber atrophy in the denervated EDL muscle of the rats compared with the denervated controls. The type I muscle fibers of both the denervated groups were similar to that of the control rats.

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脱神経筋萎縮に対する他動的関節運動の効果

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