Review article

Effects of immobilization on rat skeletal muscle tissue

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Abstract

This paper offers a literature review on the effects of immobilization on rat skeletal muscle tissue. The authors were unanimous with regard to the reduction in muscle mass, cross-section area and myonuclei in the muscles studied, especially in relation to the alteration in the regulation of the protein synthesis and degradation process as well as an alteration in the activity of oxidative enzymes caused by immobilization. With regard to the muscle fiber type, most authors report having found a greater amount of type 2 fibers over type 1 fibers, thereby implying an alteration in the contractile function of the affected muscle. These findings suggest greater degradation and/or substitution of tonic (postural or type 1) fibers by phasic (rapid contraction or type 2) fibers. Thus, the present study suggests that, regardless of the method employed, immobilization has harmful effects on skeletal muscle tissue in rats.

Keywords: immobilization, skeletal muscle, morphology, atrophy.

1 Introduction

The immobilization of parts of the body results in poor functioning and/or atrophy induced by the disuse of muscles and/or muscle groups, impairing the control and motor activities developed by this tissue (ROY et al., 2000; FITTS et al., 2001). Skeletal muscle tissue is known to be the most plastic and responsive of the bodily tissues, the phenotype of which can be molded through diverse stimuli and pathological or physiological conditions. During periods of inactivity, disuse leads to degenerative alterations in the muscle fibers (MUSACCHIA, STEFFEN and FELL, 1988). The immobilization of joints can have harmful effects on skeletal muscle tissue, such as hypotrophy, and can cause an increase in the connective tissue between and round muscle fibers as well as the loss of muscle extendibility and limitations to joint movement (WILLIAMS et al., 1988; APPELL, 1990; JARVINEN et al., 2002; SILVA et al., 2006).

Hypertrophy or muscle atrophy is a frequent condition found in both humans and animals alike in response to a variety of physiological and pathological stimuli (MITCHELL and PAVLATH, 2001; JACKMAN and KANDARIAN, 2004). Such stimuli may be associated to clinical conditions related to orthopedic conditions, such as torn ligaments, bone fractures, medullary and muscle injuries, inflammatory processes, degenerative joint processes and muscle diseases, as well as patients confined to bed for long periods of time, astronauts/cosmonauts and individuals who wear limb braces (SILVA et al., 2006; MAYR et al., 1999; REARDON et al., 2001).

In an effort to maintain homeostasis, the human body generates a biological response through a dynamic balance between the processes of protein synthesis and degradation (MITCH and GOLDBERG, 1996; LECKER et al., 1999; HORNBERGER and ESSER, 2004). The processes responsible for triggering muscle atrophy are related to a reduction in protein synthesis, an alteration in the activity of oxidative enzymes and a reduction in protein degradation (MUJIKA and PADILLA, 2001; GLASS, 2003; SASA et al., 2004; HUDSON and FRANKLIN, 2002). Such processes characterize muscle hypotrophy by reductions in protein content, muscle strength and cross-section area as well as an alteration in muscle fiber type (DIAZ-HERRERA et al., 2001; THOMPSON, 2002; KASPER, TALBOT and GAINES, 2002; JACKMAN and KANDARIAN, 2004; ROSANT, NAGEL and PÉROT, 2006).

The aim of the present study was to carry out a literature review in order to analyze morphological alterations in skeletal muscle tissue stemming from atrophy caused by different periods and methods of immobilization. The analysis addresses the effects of morphological alterations on muscle mass, cross-section area, number of myonuclei and the type 1 and type 2 fiber relations. The results and causal factors of the harmful effects of immobilization on striated skeletal muscle are discussed.

1.1 Effects of morphological alterations on muscle mass

Skeletal muscle tissue mass in adults is determined by the protein synthesis and degradation ratio (GREENHAFF, 2006). The initial adaptive responses of skeletal muscle to disuse are apparently a reduction in protein synthesis, an increase in protein degradation and a reduction glycogen content, which contribute toward a reduction in muscle mass and contractibility (LINDERMAN et al., 1994; BODINE et al., 2001; GLASS, 2003; SILVA et al., 2006; ZHONG, LOWE and THOMPSON, 2006). Different periods of immobilization can cause different degrees of hypotrophy. With as little as

one day of immobilization, there can be an approximately 8% reduction in mass in the gastrocnemius muscle, whereas this reduction can reach 19% after three days and as high as 20 to 30% after five days of immobilization. The acceptability of the progression of atrophy due to disuse is founded on the alteration in the protein metabolism, which involves both a reduction in synthesis and an increase in degradation (KRAWIEC et al., 2005). In one study, the soleus muscle of rats exhibited a 34% reduction in weight after seven days of immobilization with a resin brace in comparison to a control group, thereby suggesting proteolytic activity stemming from disuse and the osmotic mobilization of active energy reserves (SILVA et al., 2006).

During immobilization, the transcription levels of mRNA are reduced in an accentuated fashion in postural (tonic) muscles. Such levels are expressed through the production of the myosin heavy chain, the regulation of which is altered in rats that have had their legs immobilized for seven days, leading to a 36.3% reduction in the mass of the soleus muscle (GIGER et al., 2005). Despite using different methods of immobilization, Fournier et al. (1998), Itai, Kariya and Hoshino (2004), and Booth and Seider (1979) confirm these findings, as these authors respectively found a 55, 52 and 53% reduction in muscle in rats immobilized for different periods of time (28 days, 5 weeks and 12 weeks, respectively).

1.2 Effects on cross-section area

The atrophy process causes a diversity of alterations in the muscle fibers, including sarcomere dissolution, endothelial degradation, the buildup of connective tissue between muscle fibers, accentuated reduction in the number of mitochondria, elimination of apoptotic myonuclei and a reduction in capillary density (OKY et al., 1995; SMITH et al., 2000; MUJIKA and PADILLA, 2001; HUDSON and FRANKLIN, 2002) These alterations lead to a reduction in the cross-section area of the muscle fiber when the muscle is submitted to atrophic conditions (MUJIKA and PADILLA, 2001; HUDSON and FRANKLIN, 2002). The minimal action of gravity can have harmful effects on skeletal muscle in astronauts, with a 26% reduction in cross-section area in type 2a fibers and 15% reduction in type 1 fibers (EDGERTON et al., 1995; WIDRICK et al., 1999).

The confinement of patients to bed for long periods is another situation that can lead to alterations in muscle fiber area. Kawashima et al. (2004) report a reduction in the cross-section area of the short adductor muscle in patients confined to a bed for 20 days. Muscles damaged by disuse can be restored to their original size after ambulation is restored for a certain period. Consequently, the production of muscle strength is proportional to the number of days in which the muscle is submitted to disuse (BAMMAN et al., 1998). The reduction in cross-section area of the muscle fibers is due to atrophic conditions, which may affect muscle strength and locomotor activity (HUDSON and FRANKLIN, 2002).

1.3 Reduction in the number of myonuclei

The disappearance of myonuclei is one of the pathological signs of muscle atrophy (HIKIDA et al., 1997; MITCHELL and PAVLATH, 2001; MACHIDA and BOOTH, 2004b). Using rats with immobilized hind legs, Dupont-Versteegden et al. (1999, 2000) and Smith et al. (2000) found a reduction in the number of skeletal muscle fibers. Machida and Booth (2004b) report that this reduction occurs together with a reduction in cross-section area. However, a number of studies suggest that the reduction in myonuclei is not always proportional to the reduction in cross-section area (SMITH et al., 2000; ALLEN et al., 1996,1997). Due to the difference in the ratio of the different types of skeletal muscle fibers, the loss of myonuclei is greater in one type of fiber than the others (EDGERTON et al., 2002). Slow contracting muscle fiber (type 1) in rats contains a greater number of myonuclei per unit of length than type 2 fibers (ALLEN et al., 1996). Studies involving microscopy and adults rats submitted to conditions of atrophy have demonstrated that type 1 fibers undergo a greater loss of myonuclei than type 2 fibers (HIKIDA et al., 1997; BIGARD et al., 1997). Analyzing muscles in humans whose lower limbs had been immobilized, Mitchell and Pavlath (2001) and Hikida et al. (1997) found a greater reduction in the number of myonuclei in type 1 fibers of the soleus muscle in comparison to type 2 fibers in the plantar muscle. Ohira et al. (2001) report a reduction in the cross-section area and number of myonuclei in the muscle fibers of newborn rats.

1.4 Relation between type 1 and type 2 fibers

Animals submitted to immobilization exhibit alterations in the contractile properties of skeletal muscles, such as an increase in maximal contraction velocity and, consequently, the strength-velocity ratio in slow contracting muscles. Such alterations coincide with an increase in the content of fast myosin or the transformation of type 1 into type 2 fibers (GARDETTO, SCHLUTER and FITTS, 1989). There are no scientific studies offering a detailed description of the effects of immobilization on muscle function together with myosin and fiber type (BERG, LARSSON and TESCH, 1997). However, Kauhanen et al. (1998) and Daugaard and Richter (2001) report that muscles made up of predominantly type 1 fibers take on properties of muscles made up of predominantly type 2 fibers after a few weeks of immobilization. Tischler et al. (1993) report considerable muscle atrophy in slow-contracting fibers (type 1) in young rats submitted to minimal gravity, thereby demonstrating the effect of gravity on the maintenance of muscle tone and the morphology of type 1 fibers. In another study involving minimal gravity, Fitts et al. (2000) found a reduction in the weight of the gastrocnemius, plantar and soleus muscles (16, 24 and 38%, respectively). In rats, the slow-contracting fibers of anti-gravity muscles and the extensor group, such as the soleus and long adductor, are more affected by atrophic conditions than those of the fast-contracting muscles and flexor group (FIITS et al., 2000). Analyzing the soleus muscle after four weeks of immobilization, Booth (1982) reports an absolute reduction in the number of slow-contracting fibers, but found no significant difference in the number of fast-contracting fibers. These results corroborate those reported by Maier et al.(1976) and Edgerton et al. (2002) who also found a reduction in the proportion of slow-contracting fibers in the muscles of immobilized legs in rats. However, using the same immobilization model, Cardenas, Stolov and Hardy (1977) found no reduction in the total number of muscle fibers of the soleus muscle. A number of other studies also report no change in the absolute number

of muscle fibers (TIMSON et al., 1985; ANTONIO and GONYEA, 1993a, 1993b).

2 Conclusion

Under atrophic conditions, there is greater protein degradation than synthesis in skeletal muscle tissue. This protein degradation leads to a reduction in the protein content responsible for the maintenance of the intrinsic properties of muscle tissue. Hypotrophy, such as in conditions of reduced gravity, confinement to a bed for long periods of time and the immobilization of limbs, leads to a reduction in the cross-section area of muscles as well as a reduction in the number and domain of the nuclei. Despite the contrasting results of studies, there is also a change in the proportion of slow and fast fibers, with alterations to the characteristics of type 1 fibers, which take on the characteristics of type 2 fibers. Thus, atrophy plays an important role in pathological conditions that lead to the loss of the properties of skeletal muscle tissue.

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