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REVIEW

Atrophy and hypertrophy of skeletal muscles: structural and functional aspects

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Abstract

This review summarizes current information on structural and functional changes that occur during muscle atrophy and hypertrophy. Most published studies consider an increase in total mass of a muscle as hypertrophy, whereas a decrease in total mass of a muscle is referred to as atrophy. In hypertrophy, the rate of synthesis is much higher than the rate of degradation of muscle contractile proteins, leading to an increase in the size or volume of an organ due to enlargement of existing cells. When a muscle remains in disuse for a long period, the rate of degradation of contractile proteins becomes greater than the rate of replacement, resulting in muscle atrophy. This defect may occur as a result of lack of nutrition, loss of nerve supply, micro-gravity, ageing, systemic disease, prolonged immobilization or disuse. An understanding of the specific modifications that occur during muscle atrophy and hypertrophy may facilitate the development of novel techniques, as well as new therapies for affected muscles.

Keywords atrophy, functional change, hypertrophy, structural change.

Atrophy and hypertrophy are two opposite conditions that can be found in pathological or diseased muscles. Atrophy is characterized by a wasting or loss of the muscle mass (A1) and usually involves a decrease in the size or cross-sectional area (CSA) (A2) of an individual myofibre or a number of myofibres (Grounds 2002). In contrast, hypertrophy is an increase in muscle mass (Russell *et al.* 2000) and CSA (Russell *et al.* 2000, Grounds 2002), specifically due to an increase in the CSA of individual muscle fibres (Grounds 2002). As a result, the muscle strength (A3) and the bone mass (Fluckey *et al.* 2002) are significantly affected.

To maintain homeostasis, the biological response of the human body generates a dynamic balance between synthetic and degradative processes (Mitch & Goldberg 1996, Lecker *et al.* 1999a, Hornberger & Esser 2004) for both atrophic and hypertrophic muscles. This dynamic balance occurs in response to any stimuli (Hoffman & Nader 2004), due to processes that promote muscle growth via increased protein content. Moreover, it can result either from increased protein production, decreased protein breakdown, or a combination of both of these aspects of protein turnover. The processes that govern the extent of muscle atrophy are based on the magnitude of the regulated decline in rate of protein synthesis, increased level of oxidative damage (A4), and subsequent unregulated protein degradation (Hudson & Franklin 2002, Glass 2003). For example, inhibitors of the proteosome block increases in protein breakdown normally seen in atrophy (Tawa *et al.* 1997), the level of ubiquitinated conjugates increase during atrophy (Lecker *et al.* 1999b) and genes that encode various components of the ubiquitin pathway increase during atrophy (Attaix *et al.* 2001, Gomes *et al.* 2001). An increase in muscle activity stimulates the expression of a protein growth factor known as insulin-like growth factor I (IGF-I). IGF-I has been shown to be sufficient to induce hypertrophy through either autocrine or paracrine mechanisms (De Vol *et al.* 1990, Barton-Davis *et al.* 1999). IGF-I expression is

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increased during compensatory hypertrophy (De Vol *et al.* 1990) caused experimentally by removing several muscles to force those remaining to take up the resultant increase in load.

Muscle atrophy

The causes of muscle atrophy are from several sources, such as neuromuscular diseases, immobilization and denervated conditions. In addition, the muscle atrophy may also take place, secondary to some devastating injuries or common health problems (Kandarian & Stevenson 2002, Jackman & Kandarian 2004), such as spinal cord injury (SCI) (Shields 1995, Castro *et al.* 1999), ageing and various systemic diseases (A5), respectively. Moreover, the condition may be exacerbated by starvation (Mitch & Goldberg 1996, Jackman & Kandarian 2004, Lecker *et al.* 2004), micro-gravity (A6), detraining (A7), reduction in neuromuscular activity (Fitts *et al.* 2000), decreased levels of hormones (A8), increases in protein degradation (A9), decreases in protein synthesis (A10), decreases in protein content (Jackman & Kandarian 2004), and various forms of reduced use (A11).

Among acute and critically ill patients, the onset of muscle atrophy is rapid and severe, beginning within 4 h of hospitalization (Kasper *et al.* 2002). In the first few weeks during hospitalization, the antigravity or the extensor group muscles will show greater atrophy than non-antigravity or flexor group muscles (Fitts *et al.* 2000, Kasper *et al.* 2002). During extended periods of hospitalization, a prolonged unused limb leads not only to an impairment of the muscle function (A12), but also to a deleterious alteration in the muscle morphology (Bloomfield 1997), manifested in symptoms such as a decrease in muscle mass (A13), a reduction of the muscle fibre diameter (Widrick *et al.* 1997, Kasper *et al.* 2002), and a reduction in the overall number of muscle fibres (Kasper *et al.* 2002). Moreover, this condition may also have a negative affect on bone health by decreasing bone mineral density at the lumbar spine, femoral neck and calcaneus (Bloomfield 1997, Hasselgren 1999). Interestingly, the duration of immobility has been shown to be positively correlated with the degree of muscle atrophy (A14).

The early signs of muscle atrophy found in these patients are accompanied by general weakness (A15) and fatigue (A16), especially in the lower limb (A17). In fact, these clinical signs may be caused either by the medication or pathological condition *per se*. Therefore, it is inappropriate to conclude the patient's condition based only on muscle testing alone. Some other clinical assessments such as electrodiagnosis, computerized muscle strength analysis and biochemical analyses are essential for providing verification and further confirmation of the status of the muscles in question. The clinical assessments for disuse muscle atrophy can be performed at the bedside, accompanied with the strength assessment by observing muscle movement, muscle tone, muscle size and muscle strength.

Changes in muscle atrophy

Muscle fibre CSA

At the cellular level, there are some noticeable changes in the muscle cell including sarcomere dissolution and endothelial degradation (Oki *et al.* 1995). In addition, there is a marked reduction in the number of mitochondrias (Rifenberick *et al.* 1973, Mujika & Padilla 2001), accumulation of connective tissue (Oki *et al.* 1995), elimination of apoptotic myonuclei (Smith *et al.* 2000), and a decrease in capillary density and signs of tortuosity (Hudson & Franklin 2003).

The general appearance indicates a noticeable reduction in the muscle fibre CSA when the muscle is in an atrophic condition (A18). Edgerton *et al.* (1995) have studied a tendency towards of muscle fibre atrophy in three astronauts using tissue biopsies obtained from the *vastus lateralis* muscle. They found a significant reduction in the muscle fibre CSA as well as a marked decrease in the type IIb > type IIa > type I fibres, respectively, after these astronauts spent 11 days in a micro-gravity environment in space. In addition, Widrick *et al.* (1999) took tissue biopsies of the *soleus* muscle from four astronauts on the 45th day before spaceflight (SF) and made a comparison with the samples taken from the 17th day of SF. They found a similar reduction as previously reported by Edgerton *et al.* (1995) in which the type IIa and the type I fibre CSA had declined by 26% and 15%, respectively. Moreover, Kawashima *et al.* (2004) have investigated the physiological CSA of thigh adductor muscles of 10 healthy subjects (five men and five women) and found an atrophic change in these muscles following 20 days of bed rest. In this case, muscle wasting due to disuse can be restored to its original size after a 1 month period of reambulation. Consequently, the production of muscle force is proportional to the number of days of disuse (A19). The decrease in muscle fibre CSA due to the atrophic condition can affect not only the maximal force (A20) and muscle power output, but also the locomotor activity (Hudson & Franklin 2002). The degrees of muscle weakness due to SF or bed rest (LeBlanc *et al.* 1992, Fitts *et al.* 2000, Stein & Wade 2005) are correlated with the period of unloading (A21).

Myonuclear number and domain size

Disappearance of myonuclear is one of the pathological signs of muscle atrophy (A22). Studies in animals which

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have undergone SCI (Dupont-Versteegden *et al.* 1999, 2000) or hindlimb immobilization (Smith *et al.* 2000) have shown a reduction in nuclear number. In addition, Machida & Booth (2004a) have reported that this sign can be coincident with the decrease of muscle fibre CSA. However, several groups of investigators have suggested that the quantitative loss of myonuclei during muscle atrophy is not always proportional to the decrease of muscle fibre CSA, but to a smaller myonuclear domain size (Allen *et al.* 1996, 1997, Smith *et al.* 2000). Another study carried out on patients following 2–4 months of bed rest by Ohira *et al.* (1999) has also shown a distinct decrease in myonuclear domain size without any change in myonuclear number. Due to the difference in the muscle fibre type ratios, the question regarding myonuclear loss is whether specific fibre types are more or less sensitive to myonuclear shifts in comparison with the others (Edgerton *et al.* 2002). The slow or type I myosin heavy chain-expressing (MHC-expressing) fibres in rats contain a greater number of myonuclei per unit length than the fast fibres (Allen *et al.* 1996). Several microscopic studies in adult rats were able to induce an atrophic condition that demonstrated type I fibres also seem to lose more myonuclei than type II fibres (A23). Similar findings were obtained in human subjects whose leg muscles were inactive during SF or hindlimb unloading (HU) (A24). These studies found a greater reduction in myonuclear number in type I MHC-expressing fibres of the *soleus* muscle when compared with the type II MHC-expressing fibres of the *plantaris* muscle. However, a study of neonatal muscle fibres in rats under the reduced weight-bearing conditions shown similar reductions in the fibre size, myonuclear number and myonuclear domain size among all fibre types (Ohira *et al.* 2001).

Muscle fibre type

After a few weeks of immobilization, muscles composed predominately of type I fibres assumed properties characteristic of type II fibres (A25). Tischler *et al.* (1993) has demonstrated that the slow-twitch fibres of the extensor muscles in young rats during SF-induced atrophy show a marked increase in susceptibility. Following a 5.4-day SF, the weights of the *gastrocnemius, plantaris* and *soleus* muscles, but not the *tibialis anterior* and *extensor digitorum longus* muscles, were decreased by 16%, 24%, and 38% respectively. In rats, the slow-twitch fibres of the antigravity and extensor group muscles, such as the *soleus* and *adductor longus* muscles, were actually more affected by atrophic conditions than the fast-twitch fibres and flexor group muscles (Fitts *et al.* 2000). Kauhanen *et al.* (1998) utilized a free microvascular muscle flap technique for 9 months and found that the mean muscle fibre diameter of the type I fibres was decreased, whereas that of the type II fibres varied from 56% to 73%. However, Booth (1982) found an absolute reduction in the number of the slow-twitch fibres, but no significant change was observed in the absolute number of the fast-twitch fibres in the cross-section of the *soleus* muscles from limbs that had experienced immobilization for 4 weeks. This finding is consistent with the subsequent reports from Edgerton *et al.* (1975) and Maier *et al.* (1976) which show a decrease in the proportion of slow-twitch fibres of the immobilized limbs. In contrast, Cardenas *et al.* (1977) employed the similar immobilized model and also reported no significant change in the total number of muscle fibres of the *soleus* muscle. These findings are supported by the results obtained from many studies which show no change in the number of fibres despite significant increase in the muscle mass (A26).

Muscle volumes

Akima *et al.* (2000) utilized a magnetic resonance imaging (MRI) technique to measure the volume of knee extensor, knee flexor and plantar flexor muscles before and after 2 weeks of SF and found similar reduction of 5.5–15.4%, 5.6–14.1% and 8.8–15.9%, respectively. In addition, they noticed that the degree of atrophy induced by the 2-week SF was greater than that induced by the 20-day bed rest. The MRI results of the SF crew members during 17 days of the mission also shown a decrease in the muscle volume of 5–17% for most muscle groups, accompanied with a loss in the bone mineral content proportional to the lean body mass by approx. 3.4–3.5% (LeBlanc *et al.* 2000). Moreover, Henriksen *et al.* (1993) have reported an increase in the interstitial fluid volume (IFV) during muscle atrophy. They suggested that the increasing IFV might be responsible for the loss of muscle mass and contractile proteins.

Amounts of muscle protein and DNA

In atrophic muscles, the amount of the contractile proteins (A27), α-actin mRNA (Babij & Booth 1988), and cytochrome *c* mRNA (Morrison *et al.* 1987, Babij & Booth 1988) are enormously reduced. By comparing per gram of the muscle mass, there is a decreased utilization of β-hydroxybutyrate, palmitate and glucose, and levels of high-energy phosphates decline (Booth 1977), as do levels of oxidative enzymes (Sasa *et al.* 2004) such as citrate synthase (Bebout *et al.* 1993), malate dehydrogenase (Rifenberick *et al.* 1973), and phosphokinase (Carmeli *et al.* 1993). In rats, the first week of muscle wasting with HU is primarily caused by a decline in protein synthesis, whereas myofibril

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degradation does not reach its maximum until days 9–15 (Thomason *et al.* 1989). Moreover, the responses of the tissue-cultured myofibres to SF were quite similar to that reported for humans and animals in space (Vandenburgh *et al.* 1999). Thus, there is little alteration in muscle protein degradation rates (Stein & Schluter 1997, Vandenburgh *et al.* 1999), or muscle metabolic rates (Miu *et al.* 1990, Vandenburgh *et al.* 1999), and there is preferential loss of myofibrillar proteins (A28). In the case of muscle fibres, the DNA fragmentation and nuclear destruction would eliminate some unneeded myonuclei, while leaving the remaining myonuclei and the fibre itself relatively unharmed (Edgerton *et al.* 2002). Evidence for DNA fragmentation and transformations in myonuclear morphology indicative of apoptosis were observed in the muscle fibres of hindlimb suspended rats (Vandenburgh *et al.* 1989), denervated rats (Vandenburgh *et al.* 1990), as well as in immobilized rabbit muscle (Smith *et al.* 2000).

Muscle disuse is a pathological condition that affects not only the biochemical and cellular levels, but also the locomotive behaviour level. In addition, some of the structural changes associated with muscle disuse atrophy are pathological and prolonged recovery periods are often required before full muscle and locomotion performance is re-established (Hudson & Franklin 2002). The studies in frogs (St-Pierre *et al.* 2000, Hudson & Franklin 2002), and some hibernating mammals such as bears (Harlow *et al.* 2001) and rats (Booth & Seider 1979) have shown that disused muscles actually require a long period time (3–4 months) of recovery to re-establish their strength and locomotor performance.

Muscle hypertrophy

Hypertrophy of a muscle is a multidimensional process involving several factors such as growth factors (GFs) (Adams & Haddad 1996, Semsaria *et al.* 1999), IGFs (A29), clenbuterol (Argiles *et al.* 2001), anabolic steroids (Beiner *et al.* 1999, Argiles *et al.* 2001), hormones (A30), the immune system (Shephard & Shek 1998), and satellite cells (A31). For example, in a study investigating IGF-I peptide levels in human muscle following 10 weeks of strength training in old men and women (aged 72–98 years), it was shown that there was a *c.* 500% increase in the levels of IGF-I within the muscle fibres of these subjects after the training period, as determined using immunohistochemistry (Singh *et al.* 1999). This demonstrates that the peptide levels in older muscles may adapt over the longer-term to exercise training. Indeed, the results of longitudinal strength training studies have confirmed that the muscles of even very elderly people are able to exhibit a hypertrophy response to resistance exercise (A32).

IGF-I is also thought to be involved in the activation of satellite cells (Barton-Davis *et al.* 1999, Machida & Booth 2004a), satellite cells are small mononucleate muscle stem cells located between the sarcolemma and basal lamina of muscle fibres. Recently, the link between satellite cell number and myofibre size has been demonstrated in both untrained and hypertrophied human muscle fibres (Kadi & Thornell 2000). These cells, when activated, are believed to proliferate and differentiate into myoblasts, which then fuse with existing fibres, thus providing new nuclei to maintain the ratio of DNA to protein for fibres undergoing hypertrophy. The link between IGF-I, satellite cells, and hypertrophy has been shown in studies where localised infusion of IGF-I into the *tibialis anterior* muscle of adult rats resulted in an increased total muscle protein and DNA content (Adams & McCue 1998). More recently, Bamman *et al.* (2001) reported a 62% increase in IGF-I mRNA concentration in human muscle 48 h after a single bout of eccentric resistance type exercise.

Changes in muscle hypertrophy

Muscle fibre CSA

Myofibre CSA increases during overload-induced hypertrophy of a muscle. Radial enlargement of muscle fibres after resistance training or external loading confers to the muscle a greater potential for maximal force production. During load-induced myofibre hypertrophy there is an increased accumulation of contractile and non-contractile muscle proteins, and the synthesis and degradation rates of these proteins are critical for determining their net quantity (Goldspink 1991). Protein synthesis and degradation rates have been shown to be altered in hypertrophying muscle (Goldberg 1969, Laurent *et al.* 1978).

Overload-induced hypertrophy is a complex event, but the research in this area supports a two-stage model of muscle adaptation to overload: (1) during regulation at the onset of hypertrophy, muscle protein synthesis increases during overload-induced muscle hypertrophy in both humans and animals (A33). Wong & Booth (1990) found that the major mediator of increased myofibril protein synthesis in the rat *gastrocnemius* muscle after acute isotonic resistance exercise was not RNA abundance, but most likely increased RNA activity (g protein per μg RNA); and (2) during regulation at later stages of hypertrophy, myofibrillar protein mRNA levels increase later from overload-induced enlargement in most hypertrophy models. Skeletal α-actin mRNA has been shown to increase between 3 and 6 days of chronic stretch overload (Carson *et al.* 1996). The increased mRNA template can be achieved by increasing the transcription rate of

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the given gene and/or the addition of a satellite cell derived nuclei. Kadi *et al.* (2004) have demonstrated that the high plasticity of satellite cells in response to training, providing new insights into the long-term effects of training followed by detraining. This research has shown that moderate changes in the size of muscle fibres can be achieved without the addition of new myonuclei, which indicates that existing myonuclei are able to support a certain level of muscle fibre hypertrophy. Hypertrophying muscles appear to be sensitive to both loading conditions and the muscle fibre's microenvironment, both of which govern the degree of enlargement that the muscle fibre has achieved. Integrins are proteins which connect the extracellular matrix to the cytoskeleton by spanning the sarcolemma. These integrins play a role as receptors, so that alterations in cell shape are a result of mechanical signals which have been shown to alter gene expression in the nucleus, and integrin receptors may play a prominent role in this pathway (Schwartz & Ingber 1994).

Skeletal muscle fibres have a remarkable ability to alter their phenotype in response to environmental stimuli or perturbations. An example of this capacity for adaptive change, or plasticity, is the cell hypertrophy that occurs after resistance training. There is a general consensus that resistance training causes hypertrophy of all muscle fibre types, with fast fibres often showing a somewhat greater response than slow fibres (A34). In addition, McCall *et al.* (1996) have reported that the pattern of hypertrophy differed between the type I and II fibres. In the type I population, the hypertrophy occurred in the medium size fibres, whereas the entire range of fibres underwent hypertrophy in the type II population. Finally, the distribution of type II fibres was much wider than that of type I fibres, both before and after training. Other studies in human muscle fibres have reported that the CSA of *vastus lateralis* muscle fibres containing type I, IIa or IIa/IIx MHC increased by an average of 30% after 36 resistance training sessions (Widrick *et al.* 2002). These data are consistent with the resistance training-induced increases in slow- and fast-fibre CSA reported in the histochemical literature (A35).

Muscle fibre type

The effects of transgenic or exercise-induced hypertrophy on shifts in muscle fibre type were investigated by scoring the percentage of type I, type IIb and type IIa/x MHC-positive fibres in *gracilis anterior* and *gracilis posterior* muscles. Minimal fibre type changes have been observed previously in the myosin light chain/mIGF-I transgenic mice (Musaro *et al.* 2001), whereas significant fibre type changes have been observed with voluntary exercise (Allen *et al.* 2001). In addition, Paul & Rosenthal (2002) have investigated these fibre transmutations in two mouse gracilis muscles, in response to expression of a muscle-specific IGF-I transgene (mIGF-I) or to chronic exercise. The *gracilis anterior* muscle shown decreased type I and type IIa/x MHC-positive fibres, with an increase in type IIb MHC-positive fibres, although the trend was not statistically significant. Exercise, rather than the expression of the myosin light chain/mIGF-I transgene appears to be the determinant of fibre type changes in this muscle, since only muscles from the wild-type-exercise and IGF-exercise have shown a significant increase in type IIb MHC-positive fibres. The *gracilis posterior* muscle also has shown a slight decrease in the number of type I MHC-positive fibres with a trend toward a greater number of type IIa/x MHC-positive fibres at the cost of type IIb fibres. The preferential increase in type IIa/x over type IIb-positive fibres in this muscle compare with the *gracilis anterior* muscle likely reflects the specific activity patterns and loading of these muscles. These results indicated that the proportion of fibre phenotype is predominantly influenced by exercise in both the single and the multiple-innervated muscle.

Muscle volume

A pronounced adaptive response to high-intensity or weight bearing exercise interventions is muscle hypertrophy. The increased mass of active muscle groups is achieved by an increase in the volume of individual myofibres (Green *et al.* 1999). The enlarged myofibre can only expand with the insertion of new nuclei, because a constant ratio of nuclei to cytoplasmic volume is maintained throughout all hypertrophic responses (McCall *et al.* 1998, Barton-Davis *et al.* 1999). Thus, hypertrophy is dependent on the proliferative activation of satellite cells and their myogenic differentiation (Seale & Rudnicki 2000) before fusion with the existing myofibre (Garry *et al.* 2000). Another study observed in 60 healthy men (aged 18–35 years) treated with graded doses of testosterone are associated with concentration-dependent increases in CSA of both type I and type II muscle fibres and myonuclear number. They concluded that the testosterone-induced increase in muscle volume can be attributed to muscle fibre hypertrophy (Sinha-Hikim *et al.* 2002).

Protein synthesis

Muscle hypertrophy is a condition characterized by increasing protein accumulation in the stimulated muscle cells. It is due to an imbalance turnover rate between increased protein synthesis and the lesser protein breakdown (Hornberger & Esser 2004). It is known that a period of resistance training enhances protein

synthesis in human muscles (A36). The enhancement of protein synthesis might be mediated by pre-translational (alteration in the abundance of mRNA), translational (alteration in protein synthesis per unit of mRNA), or post-translational (transformation of the protein such as phosphorylation) events (Booth *et al.* 1998, Tipton & Wolfe 1998). It is suggested that changes in the translational efficiency are responsible for the early stages of protein synthesis enhancement (Laurent *et al.* 1978). During the later stages of protein synthesis enhancement, it appears that pre-translational events become critical (abundance of mRNA) (Adams 1998). In this respect, adult muscle fibres are multinucleated cells where each myonucleus controls the production of mRNA and protein synthesis over a finite volume of cytoplasm, a concept known as the DNA unit or myonuclear domain (Cheek 1985, Hall & Ralston 1989). There is evidence showing that a stimulation of myofibres with low-frequency, high-intensity intermittent currents produces a hypertrophic change, resulting in a 45–80% increase in total protein synthesis (Vandenburgh *et al.* 1989) and 15–30% decrease in total protein degradation (Vandenburgh *et al.* 1990). The increase in translational capacity is indicated by increased numbers of ribosomes which leads to protein expression and protein synthesis, respectively (Nader *et al.* 2002). The newly synthesized contractile proteins are likely to be incorporated into the existing myofibrils. However, there is a limit to the growth of myofibrils. After reaching this particular threshold limit, each myofibril can initiate a separation process. All together, it is generally accepted that muscle hypertrophy results primarily from the growth of individual muscle cells rather than increasing the number of muscle fibres.

Conclusion

Muscle can be characterized by two terms, hypertrophy and atrophy, depending on whether there is an increase in the total mass of a muscle or a decrease in the total mass of a muscle, respectively. In almost all cases, muscle hypertrophy results from an increase in the number of actin and myosin filaments in each muscle fibre, thus causing enlargement of individual muscle fibres, which is called fibre hypertrophy. This usually occurs in response to contraction of a muscle at near maximum force. Hypertrophy occurs to a much greater extent when the muscle is simultaneously loaded during a contractile process. It is known that the rate of synthesis is much higher than the rate of degradation of muscle contractile proteins during hypertrophy, leading to an increase in the size or volume of an organ due to enlargement of existing cells. When a muscle remains in disuse for a long period, the rate of degradation of contractile proteins occurs more rapidly than the rate of replacement, resulting in a defect called muscle atrophy. Muscle atrophy may occur from lack of nutrition, loss of nerve supply, micro-gravity, ageing, systemic diseases, as well as from prolonged immobilization or disuse. Examination of the muscle fibre may reveal a shrinking of diameter and strength, in addition to a fundamental alteration of the types of remaining muscle fibres. Antigravity muscles that frequently contract to support the body typically have a large number of slow fibres (type I), which appear to change more rapidly than fast fibres (type II) during prolonged periods of unloading. This process is often quite rapid, as one complete cycle is completed every few weeks. Details of the structural and functional changes that occur during atrophy and hypertrophy muscles, as well as mechanistic explanations for how these changes occur, are lacking. Basic questions that must be addressed in this field follow logically from the material presented herein. What are the proteins that are altered within atrophied and hypertrophied muscles? Are the signalling proteins essential to the mechanisms regulating muscle atrophy and hypertrophy? Does the muscle respond differently to varying causes of atrophy and hypertrophy? Does the age of the fibres have an influence on the atrophy and hypertrophy process affecting the properties of the muscular tissue? These are the types of questions that must ultimately be answered to develop rational therapy and rehabilitation strategies to be able to provide effective treatment to affected muscles.

Conflict of interest

There are no conflicts of interest.

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A3: Thomason & Booth (1990), Berg *et al.* (1991), Hather *et al.* (1992), LeBlanc *et al.* (1992), Edgerton *et al.* (1995), Andersen *et al.* (1999), Antonutto *et al.* (1999), Fitts *et al.* (2000), Lambertz *et al.* (2001), Widrick *et al.* (2001), Hudson & Franklin (2002), Jackman & Kandarian (2004)

A4: Mujika & Padilla (2001), Wanagat *et al.* (2001), Hudson & Franklin (2002), Glass (2003), Sasa *et al.* (2004)

A5: Mitch & Goldberg (1996), Gonzalez-Cadavid *et al.* (1998), Price & Mitch (1998), Mosoni *et al.* (1999), Baumgartner (2000), Chakravarthy *et al.* (2000), Gomes *et al.* (2001), Wanagat *et al.* (2001), Kandarian & Stevenson (2002), McDonald (2002), Deschenes (2004), Hunter *et al.* (2004), Jackman & Kandarian (2004), Lecker *et al.* (2004), Sandri *et al.* (2004)

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A13: Booth (1982), Bloomfield (1997), Vandenborne *et al.* (1998), Kandarian & Stevenson (2002), Kasper *et al.* (2002)

A14: Booth (1977), Ploutz-Snyder *et al.* (1995), Berg *et al.* (1997), Kasper *et al.* (2002)

A15: Caiozzo *et al.* (1994), Widrick *et al.* (1999), Kasper *et al.* (2002), Jackman & Kandarian (2004)

A16: Caiozzo *et al.* (1994), Edgerton *et al.* (1995), Shields (1995), Widrick *et al.* (1999), Kasper *et al.* (2002), Roy *et al.* (2002), Jackman & Kandarian (2004)

A17: Caiozzo *et al.* (1994), Bloomfield (1997), Widrick *et al.* (1999), Kasper *et al.* (2002)

A18: Desplanches *et al.* (1990), Widrick & Fitts (1997), Mujika & Padilla (2001), Widrick *et al.* (2001), Hudson & Franklin (2002)

A19: Berg *et al.* (1991,1997), Berg & Tesch (1996), Bamman *et al.* (1998)

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A21: Berg *et al.* (1991,1997), Berg & Tesch (1996), Bamman *et al.* (1998)

A22: Allen *et al.* (1996), Hikida *et al.* (1997), Mitchell & Pavlath (2001), Edgerton *et al.* (2002), Machida & Booth (2004b)

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A25: Booth (1982), Desplanches *et al.* (1990), McCarthy *et al.* (1997), Kauhanen *et al.* (1998), Daugaard & Richter (2001)
A26: Holly *et al.* (1980), Gollnick *et al.* (1981,1983), MacDougall *et al.* (1984), Timson *et al.* (1985), Antonio & Gonyea (1993a,b)
A27: Morrison *et al.* (1987), Babij & Booth (1988), Taillandier *et al.* (1996), Stein *et al.* (1999)
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A30: Izquierdo *et al.* (2001), Durand *et al.* (2003), Sinha-Hikim *et al.* (2002, 2003)
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A33: Goldspink (1977), Laurent *et al.* (1978), Wong & Booth (1990), MacDougall *et al.* (1995)
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