REVIEW
Atrophy and hypertrophy of skeletal muscles: structural and functional aspects

O. Boonyarom[1] and K. Inui[2]

1 Department of Physical Therapy, Naresuan University, Phitsanulok, Thailand
2 Department of Physical Therapy, Sapporo Medical University, Sapporo, Japan

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

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

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 diam-

eter 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

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 alter-ation 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 fragmenta-tion 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 atro-phy 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 ster-oids (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 hyper-trophy 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). Pro-tein 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 regu-lation 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

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.

References

Adams, G.R. & Haddad, F. 1996. The relationships among IGF-1, DNA content, and protein accumulation during skeletal muscle hypertrophy. *J Appl Physiol* **81**, 2509–2516.

Adams, G.R. 1998. Role of insulin-like growth factor-I in the regulation of skeletal muscle adaptation to increased loading. *Exerc Sports Sci Rev* **26**, 31–60.

Adams, G.R. & McCue, S.A. 1998. Localized infusion of IGF-I results in skeletal muscle hypertrophy in rats. *J Appl Physiol* **84**, 1716–1722.

Akima, H., Kawakami, Y., Kubo, K. *et al.* 2000. Effect of short-duration spaceflight on thigh and leg muscle volume. *Med Sci Sports Exerc* **32**, 1743–1747.

Allen, D.L., Yasui, W., Tanaka, T. *et al.* 1996. Myonuclear number and myosin heavy chain expression in rat soleus

single muscle fibers after spaceflight. *J Appl Physiol* **81**, 145–151.

Allen, D.L., Linderman, J.K., Roy, R.R., Grindeland, R.E., Mukku, V. & Edgerton, V.R. 1997. Growth hormone/IGF-I and/or resistive exercise maintains myonuclear number in hindlimb unweighted muscles. *J Appl Physiol* **83**, 1857–1861.

Allen, D.L., Harrison, B.C., Maass, A., Bell, M.L., Byrnes, W.C. & Leinwand, L.A. 2001. Cardiac and skeletal muscle adaptations to voluntary wheel running in the mouse. *J Appl Physiol* **90**, 1900–1908.

Alway, S.E., MacDougall, J.D. & Sale, D.G. 1989. Contractile adaptations in the human triceps surae after isometric exercise. *J Appl Physiol* **66**, 2725–2732.

Andersen, J.L., Gruschy-Knudsen, T., Sandri, C., Larsson, L. & Schiaffino, S. 1999. Bed rest increases the amount of mismatched fibers in human skeletal muscle. *J Appl Physiol* **86**, 455–460.

Antonio, J. & Gonyea, W.J. 1993a. Role of muscle fiber hypertrophy and hyperplasia in intermittently stretched avian muscle. *J Appl Physiol* **74**, 1893–1898.

Antonio, J. & Gonyea, W.J. 1993b. Skeletal muscle fiber hyperplasia. *Med Sci Sports Exercise* **25**, 1333–1345.

Antonutto, G., Capelli, C., Girardis, M., Zamparo, P. & di Prampero, P.E. 1999. Effects of microgravity on maximal power of lower limbs during very short efforts in humans. *J Appl Physiol* **86**, 85–92.

Argiles, J.M., Meijsing, S.H., Pallares-Trujillo, J., Guirao, X. & Lopez-Soriano, F.J. 2001. Cancer cachexia: a therapeutic approach. *Med Res Rev* **21**, 83–101.

Attaix, D., Combaret, L., Pouch, M.N. & Taillandier, D. 2001. Regulation of proteolysis. *Curr Opin Clin Nutr Metab Care* **4**, 45–49.

Babij, P. & Booth, F.W. 1988. α-Actin and cytochrome *c* mRNAs in atrophied adult rat skeletal muscle. *Am J Physiol* **254**, C651–C656.

Baldwin, K.M., Herrick, R.E., Ilyina-Kakueva, E. & Oganov, V.S. 1990. Effects of zero gravity on myofibril content and isomyosin distribution in rodent skeletal muscle. *FASEB J* **4**, 79–83.

Baldwin, K.M. 1996. Effect of spaceflight on the functional, biochemical, and metabolic properties of skeletal muscle. *Med Sci Sports Exerc* **28**, 983–987.

Bamman, M.M., Clarke, M.S.F., Feeback, D.L. *et al.* 1998. Impact of resistance exercise during bed rest on skeletal muscle sarcopenia and myosin isoform distribution. *J Appl Physiol* **84**, 157–163.

Bamman, M.M., Shipp, J.R., Jiang, J. *et al.* 2001. Mechanical load increases muscle IGF-I and androgen receptor mRNA concentrations in humans. *Am J Physiol* **280**, E383–E390.

Barton-Davis, E.R., Shoturma, D.I. & Sweeney, H.L. 1999. Contribution of satellite cells to IGF-I induced hypertrophy of skeletal muscle. *Acta Physiol Scand* **167**, 301–305.

Baumgartner, R.N. 2000. Body composition in healthy aging. *Ann N Y Acad Sci* **904**, 437–448.

Bebout, D.E., Hogan, M.C., Hempleman, S.C. & Wagner, P.D. 1993. Effects of training and immobilization on $V̇_{O_2}$ and D_{O_2} in dog gastrocnemius muscle in situ. *J Appl Physiol* **74**, 1697–1703.

Beiner, J.M., Jokl, P., Cholewicki, J. & Panjabi, M.M. 1999. The effect of anabolic steroids and corticosteroids on healing of muscle contusion injury. *Am J Sports Med* **27**, 2–9.

Berg, H.E., Dudley, G.A., Haggmark, T., Ohlsen, H. & Tesch, P.A. 1991. Effects of lower limb unloading on skeletal muscle mass and function in humans. *J Appl Physiol* **70**, 1882–1885.

Berg, H.E. & Tesch, P.A. 1996. Changes in muscle function in response to 10 days of lower limb unloading in humans. *Acta Physiol Scand* **157**, 63–70.

Berg, H.E., Larsson, L. & Tesch, P.A. 1997. Lower limb skeletal muscle function after 6 wk of bed rest. *J Appl Physiol* **82**, 182–188.

Bigard, A.X., Serrurier, B., Merino, D., Lienhard, F., Berthelot, M. & Guezennec, C.Y. 1997. Myosin heavy chain composition of regenerated soleus muscles during hindlimb suspension. *Acta Physiol Scand* **161**, 23–30.

Bloomfield, S.A. 1997. Changes in musculoskeletal structure and function with prolonged bed rest. *Med Sci Sports Exerc* **29**, 197–206.

Bodine, S.C., Latres, E., Baumhueter, S. *et al.* 2001. Identification of ubiquitin ligases required for skeletal muscle atrophy. *Science* **294**, 1704–1708.

Booth, F.W. 1977. Time course of muscular atrophy during immobilization of hindlimbs in rats. *J Appl Physiol* **43**, 656–661.

Booth, F.W. & Seider, M.J. 1979. Recovery of skeletal muscle after 3 mo of hindlimb immobilization in rats. *J Appl Physiol* **47**, 435–439.

Booth, F.W. 1982. Effect of limb immobilization on skeletal muscle. *J Appl Physiol* **52**, 1113–1118.

Booth, F.W., Tseng, B.S., Fluck, M. & Carson, J.A. 1998. Molecular and cellular adaptation of muscle in response to physical training. *Acta Physiol Scand* **162**, 343–350.

Caiozzo, V.J., Baker, M.J., Herrick, R.E., Tao, M. & Baldwin, K.M. 1994. Effect of spaceflight on skeletal muscle: mechanical properties and myosin isoform content of a slow muscle. *J Appl Physiol* **76**, 1764–1773.

Cardenas, D.D., Stolov, W.C. & Hardy, R. 1977. Muscle fiber number in immobilization atrophy. *Arch Phys Med Rehabil* **58**, 423–426.

Carmeli, E., Hochberg, Z., Livne, E. *et al.* 1993. Effect of growth hormone on gastrocnemius muscle of aged rats after immobilization: biochemistry and morphology. *J Appl Physiol* **75**, 1529–1535.

Carson, J.A., Schwartz, R.J. & Booth, F.W. 1996. SRF and TEF-1 control of chicken skeletal α-actin gene during slow-muscle hypertrophy. *Am J Physiol* **270**, C1624–C1633.

Castro, M.J., Apple, D.F. Jr, Staron, R.S., Campos, G.E.R. & Dudley, G.A. 1999. Influence of complete spinal cord injury on skeletal muscle within 6 mo of injury. *J Appl Physiol* **86**, 350–358.

Chakravarthy, M.V., Davis, B.S. & Booth, F.W. 2000. IGF-I restores satellite cell proliferative potential in immobilized old skeletal muscle. *J Appl Physiol* **89**, 1365–1379.

Cheek, D.B. 1985. The control of cell mass and replication: the DNA unit-a personal 20-year study. *Early Hum Dev* **12**, 211–239.

Coleman, M.E., DeMayo, F., Yin, K.C. *et al.* 1995. Myogenic vector expression of insulin-like growth factor I stimulates

muscle cell differentiation and myofiber hypertrophy in transgenic mice. *J Biol Chem* **270**, 12109–12116.

Coyle, E.F., Martin, W.H. III., Sinacore, D.R., Joyner, M.J., Hagberg, J.M. & Holloszy, J.O. 1984. Time course of loss of adaptations after stopping prolonged intense endurance training. *J Appl Physiol* **57**, 1857–1864.

Daugaard, J.R. & Richter, E.A. 2001. Relationship between muscle fibre composition, glucose transporter protein 4 and exercise training: possible consequences in non-insulin-dependent diabetes mellitus. *Acta Physiol Scand* **171**, 267–276.

Deschenes, M.R. 2004. Effects of aging on muscle fibre type and size. *Sports Med* **34**, 809–824.

Desplanches, D., Mayet, M.H., Ilyina-Kakueva, E.I., Sempore, B. & Flandrois, R. 1990. Skeletal muscle adaptation in rats flown on Cosmos 1667. *J Appl Physiol* **68**, 48–52.

De Vol, D.L., Rotwein, P., Sadow, J.L., Novakofski, J. & Bechtel, P.J. 1990. Activation of insulin-like growth factor gene expression during work-induced skeletal muscle growth. *Am J Physiol* **259**, E89–E95.

Dupont-Versteegden, E.E., Murphy, R.J.L., Houle, J.D., Gurley, C.M. & Peterson, C.A. 1999. Activated satellite cells fail to restore myonuclear number in spinal cord transected and exercised rats. *Am J Physiol* **277**, C589–C597.

Dupont-Versteegden, E.E., Murphy, R.J.L., Houle, J.D., Gurley, C.M. & Peterson, C.A. 2000. Mechanisms leading to restoration of muscle size with exercise and transplantation after spinal cord injury. *Am J Physiol* **279**, C1677–C1684.

Durand, R.J., Castracane, V.D., Hollander, D.B. *et al.* 2003. Hormonal responses from concentric and eccentric muscle contractions. *Med Sci Sports Exerc* **35**, 937–943.

Edgerton, V.R., Barnard, R.J., Peter, J.B., Maier, A. & Simpson, D.R. 1975. Properties of immobilized hind-limb muscles of the Galago senegalensis. *Exp Neurol* **46**, 15–131.

Edgerton, V.R., Zhou, M.-Y., Ohira, Y. *et al.* 1995. Human fiber size and enzymatic properties after 5 and 11 days of spaceflight. *J Appl Physiol* **78**, 1733–1739.

Edgerton, V.R., Roy, R.R., Allen, D.L. & Monti, R.J. 2002. Adaptations in skeletal muscle disuse or decreased-use atrophy. *Am J Phys Med Rehabil* **81**, S127–S147.

Ferrando, A.A., Lane, H.W., Stuart, C.A., Davis-Street, J. & Wolfe, R.R. 1996. Prolonged bed rest decreases skeletal muscle and whole body protein synthesis. *Am J Physiol* **270**, E627–E633.

Fiatarone, M.A., Marks, E.C., Ryan, N.D., Meredith, C.N., Lipsitz, L.A. & Evans, W.J. 1990. High-intensity strength training in nonagenarians: effects on skeletal muscle. *JAMA* **263**, 3029–3034.

Fiatarone, M.A., O'Neill, E.F., Ryan, N.D. *et al.* 1994. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med* **330**, 1769–1775.

Fiatarone, M.A., Ding, W., Manfredi, T.J. *et al.* 1999. Insulin-like growth factor I in skeletal muscle after weight-lifting exercise in frail elders. *Am J Physiol* **277**, E135–E143.

Fitts, R.H., Riley, D.R. & Widrick, J.J. 2000. Physiology of a microgravity environment. Invited review: microgravity and skeletal muscle. *J Appl Physiol* **89**, 823–839.

Fitts, R.H., Riley, D.R. & Widrick, J.J. 2001. Functional and structural adaptations of skeletal muscle to microgravity. *J Exp Biol* **204**, 3201–3208.

Fluckey, J.D., Dupont-Versteegden, E.E., Montague, D.C. *et al.* 2002. A rat resistance exercise regimen attenuates losses of musculoskeletal mass during hindlimb suspension. *Acta Physiol Scand* **176**, 293–300.

Franch, H.A. & Price, S.R. 2005. Molecular signaling pathways regulating muscle proteolysis during atrophy. *Curr Opin Clin Nutr Metab Care* **8**, 271–275.

Garry, D.J., Meeson, A., Elterman, J. *et al.* 2000. Myogenic stem cell function is impaired in mice lacking the *forkhead/* winged helix protein MNF. *Proc Nat Acad Sci USA* **97**, 5416–5421.

Glass, D.J. 2003. Signalling pathways that mediate skeletal muscle hypertrophy and atrophy. *Nat Cell Biol* **5**, 87–90.

Goldberg, A.L. 1969. Protein turnover in skeletal muscle: I and II. *J Biol Chem* **244**, 3217–3222.

Goldspink, D.F. 1977. The influence of immobilization and stretch on protein turnover of rat skeletal muscle. *J Physiol* **264**, 267–282.

Goldspink, D.F., Garlick, P.J. & McNurlan, M.A. 1983. Protein turnover measured *in vivo* and *in vitro* in muscles undergoing compensatory growth and subsequent denervation atrophy. *Biochem J* **210**, 89–98.

Goldspink, D.F. 1991. Exercise-related changes in protein turnover in mammalian striated muscle. *J Exp Biol* **160**, 127–148.

Gollnick, P.D., Timson, B.F., Moore, R.L. & Riedy, M. 1981. Muscular enlargement and number of fibers in skeletal muscles of rats. *J Appl Physiol* **50**, 936–943.

Gollnick, P.D., Parsons, D., Riedy, M. & Moore, R.L. 1983. Fiber number and size in overloaded chicken anterior latissimus dorsi muscle. *J Appl Physiol* **54**, 1292–1297.

Gomes, M.D., Lecker, S.H., Jagoe, R.T., Navon, A. & Goldberg, A.L. 2001. Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. *Proc Natl Acad Sci USA* **98**, 14440–14445.

Gonzalez-Cadavid, N.F., Taylor, W.E., Yarasheski, K. *et al.* 1998. Organization of the human myostatin gene and expression in healthy men and HIV-infected men with muscle wasting. *Proc Natl Acad Sci USA* **95**, 14938–14943.

Green, H., Goreham, C., Ouyang, J., Ball-Burnett, M. & Ranney, D. 1999. Regulation of fiber size, oxidative potential, and capillarization in human muscle by resistance exercise. *Am J Physiol* **276**, R591–R596.

Grounds, M.D. 2002. Reasons for the degeneration of ageing skeletal muscle: a central role for IGF-1 signalling. *Biogerontology* **3**, 19–24.

Hall, Z.W. & Ralston, E. 1989. Nuclear domains in muscle cells. *Cell* **59**, 771–772.

Harlow, H.J., Lohuis, T., Beck, T.D.I. & Iaizzo, P.A. 2001. Muscle strength in overwintering bears. *Nature* **409**, 997.

Harridge, S.D., Kryger, A. & Stensgaard, A. 1999. Knee extensor strength, activation, and size in very elderly people following strength training. *Muscle Nerve* **22**, 831–839.

Hasselgren, P.-O. 1999. Glucocorticoids and muscle catabolism. *Curr Opin Clin Nutr Metab Care* **2**, 201–205.

Hather, B.M., Tesch, P.A., Buchanan, P. & Dudley, G.A. 1991. Influence of eccentric actions on skeletal muscle adaptations to resistance training. *Acta Physiol Scand* **143**, 177–185.

Hather, B.M., Adams, G.R., Tesch, P.A. & Dudley, G.A. 1992. Skeletal muscle responses to lower limb suspension in humans. *J Appl Physiol* **72**, 1493–1498.

Hawke, T.J. & Garry, D.J. 2001. Myogenic satellite cells: physiology to molecular biology. *J Appl Physiol* **91**, 534–551.

Henriksen, E.J., Tischler, M.E., Woodman, C.R., Munoz, K.A., Stump, C.S. & Kirby, C.R. 1993. Elevated interstitial fluid volume in soleus muscles unweighted by spaceflight or suspension. *J Appl Physiol* **75**, 1650–1653.

Hikida, R.S., Van Nostran, S., Murray, J.D., Staron, R.S., Gordon, S.E. & Kraemer, W.J. 1997. Myonuclear loss in atrophied soleus muscle fibers. *Anat Rec* **247**, 350–354.

Hoffman, E.P. & Nader, G.A. 2004. Balancing muscle hypertrophy and atrophy. *Nat Med* **10**, 584–585.

Holly, R.G., Barnett, J.G., Ashmore, C.R., Taylor, R.G. & Mole, P.A. 1980. Stretch-induced growth in chicken wing muscles: a new model of stretch hypertrophy. *Am J Physiol* **238**, C62–C71.

Hornberger, T.A. & Esser, K.A. 2004. Mechanotransduction and the regulation of protein synthesis in skeletal muscle. *Proc Nutr Society* **63**, 331–335.

Hudson, N.J. & Franklin, C.E. 2002. Maintaining muscle mass during extended disuse: aestivating frogs as a model species. *J Exp Biol* **205**, 2297–2303.

Hudson, N.J. & Franklin, C.E. 2003. Preservation of three-dimensional capillary structure in frog muscle during aestivation. *J Anat* **202**, 471–474.

Hunter, G.R., McCarthy, J.P. & Bamman, M.M. 2004. Effects of resistance training on older adults. *Sports Med* **34**, 329–348.

Izquierdo, M., Hakkinen, K., Anton, A. *et al.* 2001. Maximal strength and power, endurance performance, and serum hormones in middle-aged and elderly men. *Med Sci Sports Exerc* **33**, 1577–1587.

Jackman, R.W. & Kandarian, S.C. 2004. The molecular basis of skeletal muscle atrophy. *Am J Physiol* **287**, C834–C843.

Jagoe, R.T. & Goldberg, A.L. 2001. What do we really know about the ubiquitin-proteasome pathway in muscle atrophy?. *Curr Opin Clin Nutr Metab Care* **4**, 183–190.

Jokl, P. & Konstadt, S. 1983. The effect of limb immobilization on muscle function and protein composition. *Clin Orthop Rel Res* **174**, 222–229.

Joyner, M.J. 2004. Skeletal muscle hypertrophy. *Exerc Sport Sci Rev* **32**, 127–128.

Kadi, F. & Thornell, L.E. 2000. Concomitant increases in myonuclear and satellite cell content in female trapezius muscle following strength training. *Histochem Cell Biol* **113**, 99–103.

Kadi, F., Schjerling, P., Andersen, L.L. *et al.* 2004. The effects of heavy resistance training and detraining on satellite cells in human skeletal muscles. *J Physiol* **558**, 1005–1012.

Kandarian, S.C. & Stevenson, E.J. 2002. Molecular events in skeletal muscle during disuse atrophy. *Exerc Sport Sci Rev* **30**, 111–116.

Kasper, C.E., Talbot, L.A. & Gaines, J.M. 2002. Skeletal muscle damage and recovery. *AACN Clin Issues* **13**, 237–247.

Kauhanen, M.S.C., Salmi, A.M., Von Boguslawsky, E.K., Leivo, I.V.V. & Asko-Seljavaara, S.L. 1998. Muscle fiber diameter and muscle type distribution following free microvascular muscle transfers: a prospective study. *Microsurg* **18**, 137–144.

Kawashima, S., Akima, H., Kuno, S.-Y., Gunji, A. & Fukunaga, T. 2004. Human adductor muscles atrophy after short duration of unweighting. *Eur J Appl Physiol* **92**, 602–605.

Kimball, S.R., Farrell, P.A. & Jefferson, L.S. 2002. Exercise effects on muscle insulin signaling and action. Invite review: role of insulin in translational control of protein synthesis in skeletal muscle by amino acids or exercise. *J Appl Physiol* **93**, 1168–1180.

Kraemer, W.J., Patton, J.F., Gordon, S.E. *et al.* 1995. Compatibility of high-intensity strength and endurance training on hormonal and skeletal muscle adaptations. *J Appl Physiol* **78**, 976–989.

Ku, Z. & Thomason, D.B. 1994. Soleus muscle nascent polypeptide chain elongation slows protein synthesis rate during non-weight-bearing activity. *Am J Physiol* **267**, C115–C126.

Lambertz, D., Perot, C., Kaspranski, R. & Goubel, F. 2001. Effects of long-term spaceflight on mechanical properties of muscles in humans. *J Appl Physiol* **90**, 179–188.

Laurent, G.J., Sparrow, M.P. & Millward, D.J. 1978. Turnover of muscle protein in the fowl: changes in rates of protein synthesis and breakdown during hypertrophy of the anterior and posterior latissimus dorsi muscles. *Biochem J* **176**, 407–417.

LeBlanc, A.D., Schneider, V.S., Evans, H.J., Pientok, C., Rowe, R. & Spector, E. 1992. Regional changes in muscle mass following 17 weeks of bed rest. *J Appl Physiol* **73**, 2172–2178.

LeBlanc, A., Lin, C., Shackelford, L. *et al.* 2000. Muscle volume, MRI relaxation times (T2), and body composition after spaceflight. *J Appl Physiol* **89**, 2158–2164.

Lecker, S.H., Solomon, V., Mitch, W.E. & Goldberg, A.L. 1999a. Muscle protein breakdown and the critical role of the ubiquitin-proteasome pathway in normal and disease states. *J Nutr* **129**, 227S–237S.

Lecker, S.H., Solomon, V., Price, S.R., Kwon, Y.-T., Mitch, W.E. & Goldberg, A.L. 1999b. Ubiquitin conjugation by the N-end rule pathway and mRNAs for its components increase in muscles of diabetic rats. *J Clin Invest* **15**, 1411–1420.

Lecker, S.H., Jagoe, R.T., Gilbert, A. *et al.* 2004. Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. *FASEB J* **18**, 39–51.

Linderman, J.K., Gosselink, K.L., Booth, F.W., Mukku, V.R. & Grindeland, R.E. 1994. Resistance exercise and growth hormone as countermeasures for skeletal muscle atrophy in hindlimb-suspended rats. *Am J Physiol* **267**, R365–R371.

Loughna, P., Goldspink, G. & Goldspink, D.F. 1986. Effect of inactivity and passive stretch on protein turnover in phasic and postural rat muscles. *J Appl Physiol* **61**, 173–179.

MacDougall, J.D., Elder, G.C.B., Sale, D.G., Moroz, J.R. & Sutton, J.R. 1980. Effects of strength training and immobilization on human muscle fibres. *Eur J Appl Physiol* **43**, 25–34.

MacDougall, J.D., Sale, D.G., Alway, S.E. & Sutton, J.R. 1984. Muscle fiber number in biceps brachii in bodybuilders and control subjects. *J Appl Physiol* **57**, 1399–1403.

MacDougall, J.D., Gibala, M.J., Tarnopolsky, M.A., MacDonald, J.R., Interisano, S.A. & Yarasheski, E. 1995. The time course for elevated muscle protein synthesis following heavy resistance exercise. *Can J Appl Physiol* **20**, 480–486.

Machida, S. & Booth, F.W. 2004a. Insulin-like growth factor 1 and muscle growth: implication for satellite cell proliferation. *Proc Nutr Society* **63**, 337–340.

Machida, S. & Booth, F.W. 2004b. Regrowth of skeletal muscle atrophied from inactivity. *Med Sci Sports Exerc* **36**, 52–59.

Maier, A., Crockett, J.L., Simpson, D.R., Saubert, I.V.C.W. & Edgerton, V.R. 1976. Properties of immobilized guinea pig hindlimb muscles. *Am J Physiol* **231**, 1520–1526.

Mayr, W., Bijak, M., Girsch, W. et al. 1999. MYOSTIM-FES to prevent muscle atrophy in microgravity and bed rest: preliminary report. *Artif Organs* **23**, 428–431.

McCall, G.E., Byrnes, W.C., Dickinson, A., Pattany, P.M. & Fleck, S.J. 1996. Muscle fiber hypertrophy, hyperplasia, and capillary density in college men after resistance training. *J Appl Physiol* **81**, 2004–2012.

McCall, G.E., Allen, D.L., Linderman, J.K. et al. 1998. Maintenance of myonuclear domain size in rat soleus after overload and growth hormone/IGF-I treatment. *J Appl Physiol* **84**, 1407–1412.

McCarthy, J.J., Fox, A.M., Tsika, G.L., Gao, L. & Tsika, R.W. 1997. β-MHC transgene expression in suspended and mechanically overloaded/suspended soleus muscle of transgenic mice. *Am J Physiol* **272**, R1552–R1561.

McDonald, C.M. 2002. Physical activity, health impairments, and disability in neuromuscular disease. *Am J Phys Med Rehabil* **81**, S108–S120.

McKoy, G., Ashley, W., Mander, J. et al. 1999. Expression of insulin growth factor-1 splice variants and structural genes in rabbit skeletal muscle induced by stretch and stimulation. *J Physiol* **516**, 583–592.

Mitch, W.E. & Goldberg, A.L. 1996. Mechanisms of muscle wasting: the role of the ubiquitin-proteasome pathway. *Mech Dis* **335**, 1897–1905.

Mitchell, P.O. & Pavlath, G.K. 2001. A muscle precursor cell-dependent pathway contributes to muscle growth after atrophy. *Am J Physiol* **281**, C1706–C1715.

Miu, B., Martin, T.P., Roy, R.R. et al. 1990. Metabolic and morphologic properties of single muscle fibers in the rat after space flight, Cosmos 1887. *FASEB J* **4**, 64–72.

Morey-Holton, E.R. & Globus, R.K. 2002. Hindlimb unloading rodent model: technical aspects. *J Appl Physiol* **92**, 1367–1377.

Morrison, P.R., Montgomery, J.A., Wong, T.S. & Booth, F.W. 1987. Cytochrome *c* protein-synthesis rates mRNA contents during atrophy and recovery in skeletal muscle. *Biochem J* **241**, 257–263.

Mosoni, L., Malmezat, T., Valluy, M.C., Houlier, M.L., Attaix, D. & Patureau Mirand, P. 1999. Lower recovery of muscle protein lost during starvation in old rats despite a stimulation of protein synthesis. *Am J Physiol* **277**, E608–E616.

Mujika, I. & Padilla, S. 2001. Muscular characteristics of detraining in humans. *Med Sci Sports Exerc* **33**, 1297–1303.

Musaro, A., McCullagh, K., Paul, A. et al. 2001. Localized IGF-I transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. *Nat Genet* **27**, 195–200.

Nader, G.A., Hornberger, T.A. & Esser, K.A. 2002. Translational control: implications for skeletal muscle hypertrophy. *Clin Orthop Rel Res* **403**, S178–S187.

Ohira, Y., Yoshinaga, T., Ohara, M. et al. 1999. Myonuclear domain and myosin phenotype in human soleus after bed rest with or without loading. *J Appl Physiol* **87**, 1776–1785.

Ohira, Y., Tanaka, T., Yoshinaga, T. et al. 2001. Ontogenetic, gravity-dependent development of rat soleus muscle. *Am J Physiol* **280**, C1008–C1016.

Oki, S., Desaki, J., Matsuda, Y., Okumura, H. & Shibata, T. 1995. Capillaries with fenestrae in the rat soleus muscle after experimental limb immobilization. *J Electron Microsc* **44**, 307–310.

Parcell, A.C., Trappe, S.W., Godard, M.P., Williamson, D.L., Fink, W.J. & Costill, D.L. 2000. An upper arm model for simulated weightlessness. *Acta Physiol Scand* **169**, 47–54.

Paul, A.C. & Rosenthal, N. 2002. Different modes of hypertrophy in skeletal muscle fibers. *J Cell Biol* **156**, 751–760.

Ploutz-Snyder, L.L., Tesch, P.A., Crittenden, D.J. & Dudley, G.A. 1995. Effect of unweighting on skeletal muscle use during exercise. *J Appl Physiol* **79**, 168–175.

Price, S.R. & Mitch, W.E. 1998. Mechanisms stimulating protein degradation to cause muscle atrophy. *Curr Opin Clin Nutr Metab Care* **1**, 79–83.

Ravaglia, G., Forti, P., Maioli, F. et al. 2000. Body composition, sex steroids, IGF-1, and bone mineral status in aging men. *J Gerontol* **55A**, M516–M521.

Reardon, K., Galea, M., Dennett, X., Choong, P. & Byrne, E. 2001. Quadriceps muscle wasting persists 5 months after total hip arthroplasty for osteoarthritis of the hip: a pilot study. *Intern Med J* **31**, 7–14.

Rennie, M.J., Wackerhage, H., Spangenburg, E.E. & Booth, F.W. 2004. Control of the size of the human muscle mass. *Annu Rev Physiol* **66**, 799–828.

Rifenberick, D.H., Gamble, J.G. & Max, S.R. 1973. Response of mitochondrial enzymes to decreased muscular activity. *Am J Physiol* **225**, 1295–1299.

Roy, R.R., Zhong, H., Hodgson, J.A. et al. 2002. Influences of electromechanical events in defining skeletal muscle properties. *Muscle Nerve* **26**, 238–251.

Russell, B., Motlagh, D. & Ashley, W.W. 2000. Form follows functions: how muscle shape is regulated by work. *J Appl Physiol* **88**, 1127–1132.

Sandri, M., Sandri, C., Gilbert, A. et al. 2004. Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. *Cell* **117**, 399–412.

Sasa, T., Sairyo, K., Yoshida, N. et al. 2004. Continuous muscle stretch prevents disuse muscle atrophy and deterioration of its oxidative capacity in rat tail-suspension models. *Am J Phys Med Rehabil* **83**, 851–856.

Schwartz, M.A. & Ingber, D.E. 1994. Integrating with integrins. *Mol Biol Cell* **5**, 389–393.

Seale, P. & Rudnicki, M. A. 2000. A new look at the origin, function, and "stem-cell" status of muscle satellite cells. *Dev Biol* **218**, 115–124.

Semsaria, C., Wu, M.-J., Ju, Y.-K. *et al.* 1999. Skeletal muscle hypertrophy is mediated by a Ca²⁺-dependent calcineurin signalling pathway. *Nature* **400**, 576–581.

Shephard, R.J. & Shek, P.N. 1998. Immune responses to inflammation and trauma: a physical training model. *Can J Physiol Pharmacol* **76**, 469–472.

Shields, R.K. 1995. Fatigability, relaxation properties, and electromyographic responses of the human paralyzed soleus muscle. *J Neurophysiol* **73**, 2195–2206.

Singh, M.A., Ding, W., Manfredi, T.J. *et al.* 1999. Insulin like growth factor-I in skeletal muscle after weight-lifting exercise in frail elders. *Am J Physiol* **277**, E135–E143.

Sinha-Hikim, I., Artaza, J., Woodhouse, L. *et al.* 2002. Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. *Am J Physiol* **283**, E154–E164.

Sinha-Hikim, I., Roth, S.M., Lee, M.I. & Bhasin, S. 2003. Testosterone-induced muscle hypertrophy is associated with an increase in satellite cell number in healthy, young men. *Am J Physiol* **285**, E197–E205.

Smith, H.K., Maxwell, L., Martyn, J.A. & Bass, J.J. 2000. Nuclear DNA fragmentation and morphological alterations in adult rabbit skeletal muscle after short-term immobilization. *Cell Tissue Res* **302**, 235–241.

Song, Y.H., Godard, M., Li, Y., Richmond, S.R., Rosenthal, N. & Delafontaine, P. 2005. Insulin-like growth factor I-mediated skeletal muscle hypertrophy is characterized by increased mTOR-p70S6K signaling without increased Akt phosphorylation. *J Investig Med* **53**, 135–142.

Staron, R.S., Malicky, E.S., Leonardi, M.J., Falkel, J.E., Hagerman, F.C. & Dudley, G.A. 1989. Muscle hypertrophy and fast fiber type conversions in heavy resistance-trained women. *Eur J Appl Physiol* **60**, 71–79.

Steffen, J.M. & Musacchia, X.J. 1986. Spaceflight effects on adult rat muscle protein, nucleic acids, and amino acids. *Am J Physiol* **251**, R1059–R1063.

Stein, T.P. & Schluter, M.D. 1997. Human skeletal muscle protein breakdown during spaceflight. *Am J Physiol* **272**, E688–E695.

Stein, T.P., Leskiw, M.J., Schluter, M.D., Donaldson, M.R. & Larina, I. 1999. Protein kinetics during and after long-duration spaceflight on MIR. *Am J Physiol* **276**, E1014–E1021.

Stein, T.P & Wade, C.E. 2005. Metabolic consequences of muscle disuse atrophy. *J Nutr* **135**, 1824S–1828S.

St-Pierre, J., Tattersall, G.J. & Boutilier, R.G. 2000. Metabolic depression and enhanced O₂ affinity of mitochondria in hypoxic hypometabolism. *Am J Physiol* **279**, R1205–R1214.

Taillandier, D., Aurousseau, E., Meynial-Denis, D. *et al.* 1996. Coordinate activation of lysosomal, Ca²⁺-activated and ATP-ubiquitin-dependent proteinases in the unweighted rat soleus muscle. *Biochem J* **316**, 65–72.

Tawa, N.E. Jr, Odessey, R. & Goldberg, A.L. 1997. Inhibitors of the proteasome reduce the accelerated proteolysis in atrophying rat skeletal muscles. *J Clin Invest* **100**, 197–203.

Taylor, W.E., Bhasin, S., Artaza, J. *et al.* 2001. Myostatin inhibits cell proliferation and protein synthesis in C₂C₁₂ muscle cells. *Am J Physiol* **280**, E221–E228.

Thomason, D.B., Biggs, R.B. & Booth, F.W. 1989. Protein metabolism and *β*-myosin heavy-chain mRNA in unweighted soleus muscle. *Am J Physiol* **257**, R300–R305.

Thomason, D.B. & Booth, F.W. 1990. Atrophy of the soleus muscle by hindlimb unweighting. *J Appl Physiol* **68**, 1–12.

Timson, B.F., Bowlin, B.K., Dudenhoeffer, G.A. & George, J.B. 1985. Fiber number, area and composition of mouse soleus following enlargement. *J Appl Physiol* **58**, 619–624.

Tipton, K.D. & Wolfe, R.R. 1998. Exercise-induced changes in protein metabolism. *Acta Physiol Scand* **162**, 377–387.

Tischler, M.E., Henriksen, E.J., Munoz, K.A., Stump, C.S., Woodman, C.R. & Kirby, C.R. 1993. Spaceflight on STS-48 and earth-based unweighting produce similar effects on skeletal muscle of young rats. *J Appl Physiol* **74**, 2161–2165.

Tomas, F.M., Munro, H.N. & Young, V.R. 1979. Effect of glucocorticoid administration on the rate of muscle protein breakdown *in vivo* in rats, as measured by urinary excretion of N^T-methylhistidine. *Biochem J* **178**, 139–146.

Tucker, K.R., Seider, M.J. & Booth, F.W. 1981. Protein synthesis rates in atrophied gastrocnemius muscles after limb immobilization. *J Appl Physiol* **51**, 73–77.

Vandenborne, K., Elliott, M.A., Walter, G.A. *et al.* 1998. Longitudinal study of skeletal muscle adaptations during immobilization and rehabilitation. *Muscle Nerve* **21**, 1006–1012.

Vandenburgh, H.H., Hatfaludy, S., Karlisch, P. & Shansky, J. 1989. Skeletal muscle growth is stimulated by intermittent stretch-relaxation in tissue culture. *Am J Physiol* **256**, C674–C682.

Vandenburgh, H.H., Hatfaludy, S., Sohar, I. & Shansky, J. 1990. Stretch-induced prostaglandins and protein turnover in cultured skeletal muscle. *Am J Physiol* **259**, C232–C240.

Vandenburgh, H., Chromiak, J., Shansky, J., Tatto, M.D. & Lemaire, J. 1999. Space travel directly induces skeletal muscle atrophy. *FASEB J* **13**, 1031–1038.

Wanagat, J., Cao, Z., Pathare, P. & Aiken, J.M. 2001. Mitochondrial DNA deletion mutations colocalize with segmental electron transport system abnormalities, muscle fiber atrophy, fiber splitting, and oxidative damage in sarcopenia. *FASEB J* **15**, 322–332.

Widrick, J.J. & Fitts, R.H. 1997. Peak force and maximal shortening velocity of soleus fibers after non-weight-bearing and resistance exercise. *J Appl Physiol* **82**, 189–195.

Widrick, J.J., Romatowski, J.G., Bain, J.L.W. *et al.* 1997. Effect of 17 days of bed rest on peak isometric force and unloaded shortening velocity of human soleus fibers. *Am J Physiol* **273**, C1690–C1699.

Widrick, J.J., Knuth, S.T., Norenberg, K.M. *et al.* 1999. Effect of a 17 day spaceflight on contractile properties of human soleus muscle fibres. *J Physiol* **516**, 915–930.

Widrick, J.J., Romatowski, J.G., Norenberg, K.M. *et al.* 2001. Functional properties of slow and fast gastrocnemius muscle fibers after a 17-day spaceflight. *J Appl Physiol* **90**, 2203–2211.

Widrick, J.J., Stelzer, J.E., Shoepe, T.C. & Garner, D.P. 2002. Functional properties of human muscle fibers after short-term resistance exercise training. *Am J Physiol* **283**, R408–R416.

Witzmann, F.A., Kim, D.H. & Fitts, R.H. 1982. Recovery time course in contractile function of fast and slow skeletal

muscle after hindlimb immobilization. *J Appl Physiol* **52**, 677–682.

Wong, T.S. & Booth, F.W. 1990. Protein metabolism in rat gastrocnemius muscle after stimulated chronic concentric exercise. *J Appl Physiol* **69**, 1709–1717.

Zhu, X., Hadhazy, M., Wehling, M., Tidball, J.G. & McNally, E.M. 2000. Dominant negative myostatin produces hypertrophy without hyperplasia in muscle. *FEBS Lett* **474**, 71–75.

Appendix: Robust References

A1: Berg *et al.* (1991), Mitch & Goldberg (1996), McCarthy *et al.* (1997), Chakravarthy *et al.* (2000), Fluckey *et al.* (2002), Grounds (2002), Machida & Booth (2004b)

A2: Thomason & Booth (1990), Hather *et al.* (1992), LeBlanc *et al.* (1992), Widrick & Fitts (1997), Andersen *et al.* (1999), Mujika & Padilla (2001), Reardon *et al.* (2001), Widrick *et al.* (2001), Grounds (2002), Hudson & Franklin (2002), Jackman & Kandarian (2004)

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)

A6: Berg *et al.* (1991), Edgerton *et al.* (1995), Allen *et al.* (1996), Baldwin (1996), Hikida *et al.* (1997), McCarthy *et al.* (1997), Antonutto *et al.* (1999), Mayr *et al.* (1999), Stein *et al.* (1999), Vandenburgh *et al.* (1999), Akima *et al.* (2000), Fitts *et al.* (2000,2001), Lambertz *et al.* (2001), Widrick *et al.* (2001), Kandarian & Stevenson (2002)

A7: Coyle *et al.* (1984), McKoy *et al.* (1999), Mujika & Padilla (2001), Joyner (2004)

A8: Price & Mitch (1998), Ravaglia *et al.* (2000), Fluckey *et al.* (2002), Franch & Price (2005)

A9: Tomas *et al.* (1979), Goldspink *et al.* (1983), Loughna *et al.* (1986), Mitch & Goldberg (1996), Taillandier *et al.* (1996), Price & Mitch (1998), Lecker *et al.* (1999a), Vandenburgh *et al.* (1999), Bodine *et al.* (2001), Gomes *et al.* (2001), Jagoe & Goldberg (2001), Taylor *et al.* (2001), Hudson & Franklin (2002), Kimball *et al.* (2002), Jackman & Kandarian (2004), Sandri *et al.* (2004), Franch & Price (2005)

A10: Tomas *et al.* (1979), Tucker *et al.* (1981), Loughna *et al.* (1986), Ku & Thomason (1994), Ferrando *et al.* (1996), Mitch & Goldberg (1996), Lecker *et al.* (1999a), Mosoni *et al.* (1999), Stein *et al.* (1999), Vandenburgh *et al.* (1999), Fitts *et al.* (2000), Taylor *et al.* (2001), Hudson & Franklin (2002), Jackman & Kandarian (2004)

A11: Tucker *et al.* (1981), Booth (1982), Jokl & Konstadt (1983), Loughna *et al.* (1986), Morrison *et al.* (1987), Thomason & Booth (1990), Caiozzo *et al.* (1994), Ku & Thomason (1994), Ferrando *et al.* (1996), Taillandier *et al.* (1996), Berg *et al.* (1997), Bloomfield (1997), McCarthy *et al.* (1997), Widrick & Fitts (1997), Kauhanen *et al.* (1998), Vandenburgh *et al.* (1999), Widrick *et al.* (1999), Bodine *et al.* (2001), Gomes *et al.* (2001), Reardon *et al.* (2001), Hudson & Franklin (2002), Kandarian & Stevenson (2002), Kasper *et al.* (2002), Morey-Holton & Globus (2002), Jackman & Kandarian (2004), Joyner (2004), Machida & Booth (2004b), Sandri *et al.* (2004)

A12: Berg & Tesch (1996), Fitts *et al.* (2000), Kandarian & Stevenson (2002), Jackman & Kandarian (2004)

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)

A20: Witzmann *et al.* (1982), Berg & Tesch (1996), Parcell *et al.* (2000), Mujika & Padilla (2001)

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)

A23: Allen *et al.* (1996,1997), Bigard *et al.* (1997), Hikida *et al.* (1997)

A24: Allen *et al.* (1996,1997), Hikida *et al.* (1997), Mitchell & Pavlath (2001)

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)

A28: Steffen & Musacchia (1986), Baldwin *et al.* (1990), Linderman *et al.* (1994), Vandenburgh *et al.* (1999)

A29: De Vol *et al.* (1990), Coleman *et al.* (1995), Adams & McCue (1998), Fiatarone *et al.* (1999), Grounds (2002), Song *et al.* (2005)

A30: Izquierdo *et al.* (2001), Durand *et al.* (2003), Sinha-Hikim *et al.* (2002, 2003)

A31: Adams & McCue (1998), Zhu *et al.* (2000), Hawke & Garry (2001), Sinha-Hikim *et al.* (2003)

A32: Fiatarone *et al.* (1990,1994), Harridge *et al.* (1999), Singh *et al.* (1999)

A33: Goldspink (1977), Laurent *et al.* (1978), Wong & Booth (1990), MacDougall *et al.* (1995)

A34: Alway *et al.* (1989), Staron *et al.* (1989), Hather *et al.* (1991), Kraemer *et al.* (1995), McCall *et al.* (1996), Green *et al.* (1999)

A35: MacDougall *et al.* (1980), Hather *et al.* (1991), Kraemer *et al.* (1995), McCall *et al.* (1996)

A36: Adams (1998), Booth *et al.* (1998), Tipton & Wolfe (1998), Rennie *et al.* (2004)