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Influence of aging and long-term unloading on the structure and function of human skeletal muscle¹

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Abstract

Understanding the quantitative and qualitative changes in skeletal muscle that control changes in function is crucial in the development of countermeasures to the loss of skeletal muscle function observed with real and simulated micro-gravity exposure (i.e., unloading) and with aging in humans. Qualitative changes that could influence the force and power producing properties of skeletal muscle are changes in the distribution of the 3 isoforms of the main motor protein myosin heavy chain (MHC), as well as the abundance of MHC, actin (the other main contractile protein), and the force distributing the connective tissue network. Numerous studies have examined quantitative and qualitative changes in skeletal muscle, from the whole muscle to the single myofiber from individuals undergoing real and simulated space flight for a few weeks to several months, as well as from aging men and women. When considering the relative content of the main functional and structural elements (i.e., myosin, actin, collagen), it appears that human muscle appropriately scales changes in size of 10%–40% induced over a relatively short time period (1–3 months) and over the lifespan (in humans 20 to 90+ years old). The main qualitative change with unloading and aging is a redistribution of the 3 MHC isoforms, which have vastly different contractile characteristics. It is now known that the response of skeletal muscle to unloading is muscle and gender specific. In summary, changes in muscle mass (quantity) combined with the alterations in MHC distribution (quality) are the primary determinants of changes in muscle function with unloading and aging. These parameters are the key components of muscle that should be targeted with countermeasures for conditions related to muscle loss, along with considerations for muscle- and gender-specific responses.

Keywords

myosin heavy chain; actin; collagen; single myofiber; bed rest; unilateral lower limb suspension; space flight; aging; sarcopenia

Introduction

The hallmark of the decreased use of skeletal muscle over several weeks or months and over the lifespan of humans is a decrease in muscle mass. Along with this loss of muscle mass is a decrease in muscle function, including a loss of muscle strength, power, and endurance. Whether intrinsic changes within the skeletal muscle contribute to the loss of muscle function, or whether the loss of mass solely controls the loss of muscle function is not clear.

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This issue becomes important as strategies (i.e., countermeasures) to prevent the decrements in muscle performance that occur with unloading and aging are considered.

Structural determinants of muscle function

Myosin and actin proteins

The generation of muscle force and power is derived from the interaction of the motor protein myosin with actin within each muscle fiber (Huxley and Niedergerke 1954; Huxley and Hanson 1954). Outside of supplying the necessary energy (ATP) to the myosin heavy chain (MHC) component of the myosin molecule (the site of the ATPase activity), the single most important determinant of muscle power is the type of MHC that is present. In humans, there are 3 types (i.e., isoforms) of MHC (type I, IIa, and IIx), which can be found in a variety of combinations within each muscle fiber (Schiaffino and Reggiani 1994, 1996). There are pure fibers that contain only 1 type of MHC (although pure IIx fibers are rare in humans), and hybrid fibers that contain 2 or more types of MHC (Gallagher et al. 2005; Williamson et al. 2001). To underscore the dominance of the type of MHC in muscle function, the power profiles of isolated single pure myofibers are shown in Fig. 1. Independent of fiber size, MHC IIa fibers produce ~6 times more power, and fibers with MHC IIx produce up to 20 times more power than MHC I fibers.

Given the large functional differences in the 3 human MHC proteins, it follows that the percentage of each of these proteins found within the muscle are critical to muscle function. However, the relative amount of both MHC and actin, the protein to which the MHC must bind to produce force and power, can also influence muscle function. If the amount of MHC per unit size or mass of the muscle is decreased, or if there are inadequate numbers of actin molecules for cross-bridge formation, the ability to produce force and power in the muscle can be altered (Carroll et al. 2004; Ingalls et al. 1998; Riley et al. 1998, 2000, 2002; Tikunov et al. 2001; Tsika et al. 1987). Thus, the relative amounts of the main contractile proteins MHC and actin, as well as the type of MHC, must be monitored to understand potential qualitative changes in muscle function with unloading and aging.

Connective tissue

The connective tissue component of the skeletal muscle is critical to transferring the force produced in the individual myofibers out to the fascia and to the tendon and bone (Huijing 1999; Kjaer 2004; Patel and Lieber 1997). The skeletal muscle connective tissue scaffold that surrounds the individual muscle fibers, muscle fiber bundles, and the whole muscle is primarily composed of collagen fibers. Within and between mature collagen fibers are enzymatically derived cross-linking molecules that give rise to the strength and characteristic ordered structure of collagen (Eyre et al. 1984; McCormick 1999; Reiser et al. 1992). Although the impact is not well established in human skeletal muscle, various isoforms of collagen do exist, and they have varying strength and functional characteristics (Goldspink et al. 1994; Kjaer 2004; Kovanen et al. 1988). Similar to the contractile elements of the muscle, accumulation or removal of this important collagen network or the cross-linking components can impact muscle function (Alnaqeeb et al. 1984; Ducomps et al. 2003; Gosselin et al. 1998; Kovanen et al. 1984; Willems et al. 2001).

Skeletal muscle changes with real and simulated microgravity exposure

Skeletal muscle mass (quantity)

The vast majority of well-controlled studies of muscle wasting in healthy humans have been Earth-based simulations of the microgravity environment of space. The most common analogs used for these studies are complete bed rest (i.e., 24 h·day⁻¹, 7 days·week⁻¹)

(Fortney et al. 1996), usually in the 6° head down tilt position to provide the appropriate gravitational vectors for the cardiovascular system and unilateral lower limb suspension (Berg et al. 1991; Tesch et al. 2004b). Studies using these models consistently show a precipitous decline in volume (i.e., mass) of the lower limb muscles during the first 2 to 4 weeks, with a continued, but leveling off, muscle volume loss over the subsequent several months (Adams et al. 2003; Alkner and Tesch 2004a, 2004b; Baldwin et al. 1996; Bamman et al. 1997; Fitts et al. 2000; Ferrando et al. 1995; Hather et al. 1992; LeBlanc et al. 1992; Schulze et al. 2002; Shackelford et al. 2004; Tesch et al. 2005; Trappe et al. 2007b). The amount of muscle loss is muscle group specific, with the upper body loss relatively small, the lower limb loss relatively large (up to ~40%), and the lower leg (i.e., triceps surae) loss the greatest (Alkner and Tesch, 2004a, 2004b; LeBlanc et al. 1992; Shackelford et al. 2004; Trappe et al. 2007b). Recent evidence also shows that women subjected to bed rest lose significantly more muscle mass and at a faster rate than men (Alkner and Tesch, 2004a, 2004b; Shackelford et al. 2004; Trappe et al. 2007b). This additional atrophy in women appears to be the result of additional atrophy of type IIa muscle fibers (Trappe et al. 2007a), at least in the thigh muscles.

Several studies have employed countermeasures in an attempt to offset or prevent the loss of muscle mass with unloading (Alkner and Tesch, 2004a, 2004b; Bamman et al. 1997, 1998; Berg et al. 1997; Greenleaf et al. 1989; Schulze et al. 2002; Shackelford et al. 2004; Tesch et al. 2005; Trappe et al. 2007b, 2009). Consistently, these studies have shown that resistance exercise performed at a relatively high intensity, but at a relatively low dose, can be highly effective at preventing the loss of muscle mass with unloading. That is, only a couple of minutes of activity per muscle group every 3 days are needed in most cases, suggesting unloaded muscle is very responsive to the hypertrophic stimulus of resistance exercise. Indeed, individuals undergoing 5 weeks of unilateral lower limb suspension with resistance training had 26% more hypertrophy than ambulatory subjects completing the same resistance training protocol (Tesch et al. 2004a, 2004b). Recent evidence also shows that aerobic exercise plays a complementary role with resistance exercise in unloaded muscle (Trappe et al. 2007a, 2007b, 2008). Aerobic exercise appears to target the type I fibers of both the quadriceps and the calf (i.e., the soleus). Interestingly, a nutrition only (i.e., without exercise) countermeasure approach of a leucine-enriched high-protein diet does not help prevent the loss of muscle mass with bed rest (Trappe et al. 2007a, 2007b, 2008). In fact, this nutritional regimen exacerbated the loss of muscle mass in women exposed to bed rest for 2 months (Trappe et al. 2007a, 2007b).

Skeletal muscle structure (quality)

Several studies have examined changes within the muscle in response to real or simulated microgravity-induced atrophy with and without countermeasures. While there appears to be some dysregulation of the relative amounts of myosin and actin in the initial stages (Riley et al. 1998, 2000, 2002), the amount of myosin, actin, and intramuscular collagen appears to scale appropriately, with atrophy of ~10%–40% in both men and women over 1 to 3 months (Haus et al. 2007a; Lemoine et al. 2009). It should be highlighted that this amount of atrophy is the most extreme amount and rate of atrophy induced in healthy humans, and is comparable to atrophy amounts observed over 50 years of aging (Trappe et al. 2001). In addition, when exercise countermeasures are employed that completely or partially offset the atrophy, or even induce significant hypertrophy during unloading, the muscle appears to appropriately regulate the relative amount of the 2 main contractile proteins (myosin and actin) and the main protein (collagen) of the intramuscular connective tissue network (Haus et al. 2007a; Lemoine et al. 2009).

The main qualitative structural change that occurs with unloading-induced atrophy over 2 to 6 months is the redistribution of the 3 MHC isoforms within each muscle fiber (Gallagher et

al. 2005; Trappe et al. 2007a, 2008a, 2009). Muscle fibers containing only the slow MHC type I are reduced, fibers with some portion of MHC IIa and IIx are increased, and the overall proportion of fibers that contain more than 1 type of MHC (i.e., a hybrid fiber) is increased (Gallagher et al. 2005; Trappe et al. 2007a, 2008a, 2009). This fiber type transition supports a faster contracting and more powerful muscle (not considering the aforementioned changes in muscle size). This transition likely results in a change in muscle metabolism, fuel use, and a more fatigable muscle. Exercise countermeasures are able to partially or completely prevent this shift in MHC profile (Gallagher et al. 2005; Trappe et al. 2007a, 2008a, 2009).

Skeletal muscle changes with aging

Skeletal muscle mass (quantity) and structure (quality)

Loss of skeletal muscle mass clearly plays a role in the decline in muscle function that occurs with aging (Doherty 2003; Dutta and Hadley 1995; Janssen et al. 2002; Lexell 1995). This age-related loss of muscle mass is, at least partially, due to a loss of the total number of individual muscle fibers (~30% to 50%) (Lexell 1995; Lexell et al. 1988). There is a disproportionate loss of muscle function relative to muscle size (Goodpaster et al. 2006; Haus et al. 2007b), suggesting that, in addition to changes in muscle mass and neural drive, there are potentially changes in the intrinsic functional ability of aging muscle.

Surprisingly, studies show the intrinsic power producing ability of muscle does not change with aging (Raue et al. 2009; Trappe et al. 2003) (Fig. 2). That is, power production relative to the size of the myofiber of the 2 main types of pure individual muscle fibers (MHC I and IIa) found in young and old women and men does not decline with aging. Interestingly, similar normalized single muscle fiber power has also been shown in spinal cord injured individuals (average, 15 years), compared with able-bodied controls (Malisoux et al. 2007).

The relative amounts of the main contractile proteins (MHC and actin) and connective tissue elements (collagen and the main enzymatic cross-link of collagen) are also not altered with aging (Haus et al. 2007b). These structural findings compare with the unloading literature, in that aging muscle appears to appropriately scale the relative content of the main force producing and transmitting proteins over a reduction in mass of 20%–30%. However, findings are equivocal from studies of the relative distribution of the MHC protein in aging skeletal muscle (Haus et al. 2007b; Klitgaard et al. 1990; Lexell et al. 1988). Given the known power profile of fibers containing only 1 type of the MHC isoform (Fig. 1), a shift toward more MHC I (Haus et al. 2007b) would have a significant impact on muscle function. Collectively, the literature suggests that the main contributor to the loss of muscle function with aging is a quantitative loss of muscle mass.

Conclusions

Studies of the loss of muscle mass in humans over several months or several decades show that the function of the muscle is primarily controlled by the quantity of muscle mass, while the main qualitative influence on muscle function is the relative MHC profile.

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Fig. 1.

Single muscle fiber power normalized to muscle size of muscle fibers containing only 1 type of myosin heavy chain (MHC). MHC I and IIa data come from Trappe et al. (2003), and MHC IIx data come from unpublished observations and personal communication with S. Trappe (2009). Data are means $\pm$ SE. W/L, watts per liter.

Fig. 2.

Single muscle fiber power normalized to muscle size from muscle fibers of young (25 ± 1 years) and old (79 ± 2 years; range, 70–93 years) men and women (Trappe et al. 2003). These data clearly show that when size is factored out, the power producing ability of individual MHC I and IIa fibers does not decline with age in men or women. Data are means $\pm$ SE. W/L, watts per liter.