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Review

Skeletal muscle atrophy during short-term disuse: Implications for age-related sarcopenia

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ABSTRACT

Situations such as the recovery from injury and illness can lead to enforced periods of muscle disuse or unloading. Such circumstances lead to rapid skeletal muscle atrophy, loss of functional strength and a multitude of related negative health consequences. The elderly population is particularly vulnerable to the acute challenges of muscle disuse atrophy. Any loss of skeletal muscle mass must be underpinned by a chronic imbalance between muscle protein synthesis and breakdown rates. It is recognized that muscle atrophy during prolonged (>10 days) disuse is brought about primarily by declines in post-absorptive and post-prandial muscle protein synthesis rates, without a clear contribution from changes in muscle protein breakdown. Few data are available on the impact of short-term disuse (<10 days) on muscle protein turnover in humans. However, indirect evidence indicates that considerable muscle atrophy occurs during this early phase, and is likely attributed to a rapid increase in muscle protein breakdown accompanied by the characteristic decline in muscle protein synthesis. Short-term disuse atrophy is of particular relevance in the development of sarcopenia, as it has been suggested that successive short periods of muscle disuse, due to sickness or injury, accumulate throughout an individual's lifespan and contributes considerably to the net muscle loss observed with aging. Research is warranted to elucidate the physiological and molecular basis for rapid muscle loss during short periods of disuse. Such mechanistic insight will allow the characterization of nutritional, exercise and/or pharmacological interventions to prevent or attenuate muscle loss during periods of disuse and therefore aid in the treatment of age-related sarcopenia.

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1. Introduction

Episodes of skeletal muscle inactivity, unloading or disuse often occur in (otherwise) healthy humans as a direct consequence of injury or illness. During disuse, rapid skeletal muscle loss ensues (Deitrick, 1948b; Gibson et al., 1987b; Ingemann-Hansen and Halkjaer-Kristensen, 1980) which leads to numerous negative health consequences such as impaired functional capacity and

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strength (Deitrick, 1948b; Gibson et al., 1987b; Ingemann-Hansen and Halkjaer-Kristensen, 1980; LeBlanc et al., 1992b; White et al., 1984b), the onset of insulin resistance (Stuart et al., 1988), a decline in basal metabolic rate (Haruna et al., 1994; Tzankoff and Norris, 1977) and accrual of body fat mass (Brooks et al., 2008; Ferrando et al., 1996, 1997). Furthermore, the extent of muscle loss that occurs during illness has previously been identified as an important predictor of the duration of hospitalization and subsequent need for rehabilitation (Christensen et al., 1982). Experimentally, muscle disuse atrophy in humans has generally been studied over a relatively prolonged period (>10 days) in young, healthy individuals to ensure measurable muscle loss in a practical research setting. However, an often underappreciated consideration is that signs of substantial muscle loss are already evident after only a few days of disuse. This is of great clinical significance since it is likely that the accumulation of (short) periods of muscle disuse atrophy that occur throughout an individual's lifespan contributes substantially to the etiology of age-related sarcopenia. Moreover, our understanding of the physiological mechanisms that bring about muscle atrophy over a short period of muscle disuse (<10 days) is far less comprehensive than when we consider a more prolonged period. The present review will discuss the physiological basis of skeletal muscle atrophy during prolonged and short-term muscle disuse. Particular emphasis will be placed on considering the potentially differing mechanisms which bring about short-term muscle disuse atrophy and how this relates to age-related sarcopenia.

2. Prolonged disuse atrophy (>10 days)

2.1. Basal muscle protein turnover

By far the most commonly employed models to study muscle disuse in humans over the past century have been (head down tilted) bed-rest (Deitrick, 1948a; Ferrando et al., 1996) (e.g. 25 and 35) and limb immobilization/suspension (Gibson et al., 1987a; Schoneyder et al., 1954) (e.g. 43 and 96). Such studies have shown that a period of disuse ranging between 10 and 42 days generally leads to a rate of muscle loss of approximately 0.5–0.6% of total muscle mass per day (Brooks et al., 2008; de Boer et al., 2007a; Ferrando et al., 1995; Glover et al., 2008; Hespel et al., 2001; Jones et al., 2004; Kortebein et al., 2007; Thom et al., 2001), with a variable consequent decline in muscle strength ranging between 0.3% (LeBlanc et al., 1992a; Paddon-Jones et al., 2004a) and 4.2% (Thom et al., 2001) per day. Greater relative losses of muscle strength compared with mass are likely attributed to the associated declines in neuromuscular recruitment and function that also occur with disuse (Seki et al., 2001). Given that skeletal muscle mass turns over at a relatively slow rate of ~1–2% per day, muscle disuse atrophy must ultimately be underpinned by a chronic, persistent disturbance in muscle protein balance. That is to say, for a sustained period, either muscle protein synthesis rates decline, breakdown rates increase, or a combination of both occurs. It was first demonstrated by Gibson and colleagues, utilizing contemporary stable isotope methodology, that knee immobilization for ~40 days due to cruciate knee ligament damage is accompanied by a 26% reduction in basal (fasting) muscle protein synthesis rates in young men (Gibson et al., 1987a). Disuse induced declines in basal muscle protein synthesis rates have since been replicated numerous times following 10–42 days of bed-rest (Ferrando et al., 1996, 1997, 2010; Kortebein et al., 2007; Symons et al., 2009) or lower limb immobilization (de Boer et al., 2007b; Gibson et al., 1987a, 1988; Glover et al., 2008) in younger individuals. Thus, robust evidence is available, at least in younger individuals, to show that a reduced capacity to synthesize de novo muscle proteins in the basal (fasted) state contributes to the observed loss of muscle tissue during a prolonged period of disuse.

Whether basal muscle protein breakdown rates are altered during prolonged disuse is less clear given the lack of comprehensive data. Animal models of disuse atrophy show a clear rise in muscle protein breakdown rates following the onset of disuse, which accompanies a decreased rate of muscle protein synthesis (Bodine, 2013; Lang et al., 2012; Magne et al., 2012). This parallel effect on synthesis and breakdown appears to explain the vastly greater rate of muscle loss observed in animal compared to human models of disuse (Thomason and Booth, 1990). Self-evidently, numerous differences exist between species. For instance, compared to humans, animals subjected to disuse are generally immature, metabolically unstable (i.e. homeostatic mechanisms are less tightly regulated), and in a state of stress in response to experimental interventions. Nevertheless, data from animals have led researchers to hypothesize that a rise in muscle protein breakdown may also contribute to disuse atrophy in humans. While measuring the fractional synthetic rate of infused stable isotope labeled amino acids into new muscle proteins offers a direct method for determining muscle protein synthesis rates in humans in vivo, equivalent measures for muscle protein breakdown assessment are more technically challenging and, consequently, more sparsely reported. Insight has been gained by approaches which have combined contemporary stable isotope methodology with arterio-venous balance measurements (Ferrando et al., 1996) or utilized a pulse tracer administration approach to determine fractional breakdown rates (Symons et al., 2009; Zhang et al., 1996). Such studies have concluded that muscle protein breakdown rates do not change in younger humans following 14–21 days of bed-rest. Furthermore, several studies have concluded that disuse induced impairments in muscle protein synthesis rates can quantitatively (more than) account for the observed loss of muscle mass, suggesting that muscle protein breakdown rates either do not change, or, actually adaptively decrease (Ferrando et al., 1996; Gibson et al., 1987a). Based on these data, and in contrast to similar data obtained in animal models, it has been suggested that alterations in muscle protein breakdown do not contribute to the loss of muscle tissue during prolonged disuse in humans (Phillips et al., 2009; Rennie et al., 2010). However, it is important to highlight that the quantity of available in vivo assessments of dynamic basal muscle protein breakdown rates (i.e. those data obtained from stable isotope studies) during disuse do not currently equal the insight generated on muscle protein synthesis rates.

Protein breakdown within skeletal muscle occurs via several distinct processes; most notably caspase proteases involved in apoptosis (Wang et al., 2004), cathepsins integral to autophagy (Bechet et al., 2005), the calcium-dependent calpain system (Bartoli and Richard, 2005) and the ubiquitin proteasome pathway. Though the ubiquitin proteasome pathway cannot degrade intact myofibrils (initial preprocessing of myofibrils by alternative pathways is a prerequisite for complete proteolysis), it is thought to be quantitatively the primary mediator of net skeletal muscle protein breakdown in humans (Greenhaff et al., 2008; Jagoe and Goldberg, 2001; Murton et al., 2008). During this process, specific proteins are tagged for degradation via a three-step, enzymatic, sequential cascade (Murton et al., 2008). The specificity for this targeting is afforded by the action of a family of ubiquitin ligases. Of these, the muscle specific ubiquitin ligases, muscle atrophy F-Box/atrogin-1 (MAFbx) and muscle-specific RING-finger protein 1 (MuRF1), have been shown to be transcriptionally up-regulated under numerous conditions associated with muscle atrophy (Lecker et al., 2004; Murton et al., 2008). Moreover, their specific knockout has been shown to induce partial resistance to muscle atrophy (Murton et al., 2008). While it was traditionally thought that MAFbx and MuRF1 acted in concert within a specific muscle 'atrophy program'

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