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Review

Resistance exercise and the mechanisms of muscle mass regulation in humans: Acute effects on muscle protein turnover and the gaps in our understanding of chronic resistance exercise training adaptation☆

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ABSTRACT

Increasing muscle mass is important when attempting to maximize sports performance and achieve physique augmentation. However, the preservation of muscle mass is essential to maintaining mobility and quality of life with aging, and also impacts on our capacity to recover from illness. Nevertheless, our understanding of the processes that regulate muscle mass in humans during resistance exercise training, chronic disuse and rehabilitation training following atrophy remains very unclear. Here, we report on some of the recent developments in the study of those processes thought to be responsible for governing human muscle protein turnover in response to intense physical activity. Specifically, the effects of acute and chronic resistance exercise in healthy volunteers and also in response to rehabilitation resistance exercise training following muscle atrophy will be discussed, with discrepancies and gaps in our understanding highlighted. In particular, ubiquitin-proteasome mediated muscle proteolysis (Muscle Atrophy F-box/Atrogin-1 and Muscle RING Finger 1), translation initiation of muscle protein synthesis (mammalian target of rapamycin signaling), and satellite cell mediated myogenesis are highlighted as pathways of special relevance to muscle protein metabolism in response to acute resistance exercise. Furthermore, research focused on quantifying signaling and molecular events that modulate muscle protein synthesis and protein degradation under conditions of chronic resistance training is highlighted as being urgently needed to improve knowledge gaps. These studies need to include multiple time-point measurements over the course of any training intervention and must include dynamic measurements of muscle protein synthesis and degradation and sensitive measures of muscle mass.

This article is part of a Directed Issue entitled: Muscle wasting.

Contents

1. Introduction

The maintenance of skeletal muscle mass is dependent on the balance between rates of muscle protein synthesis and muscle protein breakdown. Both of these processes are responsive to exercise, inactivity, nutrition, and inflammation and trauma, but to different degrees. Our understanding of the mechanisms regulating muscle

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protein synthesis and degradation in humans and relative contribution of each mechanism in health, aging and chronic disease remains unclear.

From a translational research perspective, impaired skeletal muscle function, particularly in the ambulatory musculature, is an important systemic feature of age related frailty. Furthermore, compared with similar aged healthy people, patients with chronic diseases, such as chronic obstructive pulmonary disease, have reduced muscle power and strength, which is usually, but not always, accompanied by muscle atrophy. Importantly, these features have a clinically relevant impact on mortality, morbidity and healthcare utilization. Also of note, impaired muscle function and mass may be remediable features of age related frailty and chronic disease, which in itself merits further investigation.

Despite the appreciation of the importance of skeletal muscle mass and function to mortality and disability in aging and chronic disease, little is known about the relative contribution of these features to the etiology of skeletal muscle dysfunction in aging and disease. Moreover, the cellular and molecular mechanisms that regulate muscle growth and atrophy in aging and chronic disease remain largely unresolved, not least because of a lack of time-course studies systematically examining cellular and molecular mechanisms regulating muscle mass and the dovetailing these observations with sensitive measures of muscle mass and muscle protein synthesis and breakdown. Similarly, whilst resistance training is effective in improving skeletal muscle mass and strength in aging and chronic disease, the mechanisms involved are relatively unknown because of a lack of detailed mechanistic based time-course studies. These are important generic issues because the identification of novel therapeutic targets and the choice of likely physical, nutritional and pharmacological therapeutic approaches in will depend upon the outcome of such studies.

Here, we report on some of the recent developments in the study of processes thought responsible for governing human skeletal muscle protein turnover in response to intense physical activity. Specifically, the effects of acute and chronic resistance exercise in health and rehabilitation training following muscle atrophy will be discussed, with discrepancies and gaps in our understanding highlighted.

2. Resistance exercise

Resistance exercise, also known as strength training, is established as an effective strategy to increase muscle mass and strength in healthy volunteers and patients. It involves muscle exerting a force against a resistance whilst contracting, and usually repetitively at a workload well above the aerobic capacity of muscle, i.e. most commonly high intensity, short lasting, fatiguing muscle contractions. However, the mechanisms of adaptation of muscle protein metabolism to acute bouts of resistance exercise and chronic resistance training programs remain unresolved.

2.1. Acute adaptations to resistance exercise

A substantial body of evidence has accumulated implicating the ubiquitin-proteasome system as a central regulator of muscle proteolysis during exercise [see Murton et al., 2008], mTOR signaling as a master regulator of translation initiation of muscle protein synthesis in response to nutrition and/or exercise [see Atherton and Smith, 2012], and satellite cell activation and proliferation in myogenesis [see Relaix and Zammit, 2012]. Indeed, all are areas of major current interest in the study of skeletal muscle adaptive responses to acute resistance exercise. For example, the mRNA levels of the ubiquitin ligase MAFbx/atrogin-1, thought important in the induction of muscle atrophy [Lecker et al., 2004], was shown to be increased in quadriceps muscle immediately following high intensity leg extension exercise, but subsequently suppressed below basal levels when examined 24 h and 72 h later [Deldicque et al., 2008]. In light of the elevated muscle protein synthesis known to occur following resistance exercise [Phillips et al., 2005], these findings might suggest protein breakdown occurs early in recovery to aid muscle-remodeling processes followed by a phase of reduced proteolysis, presumably to support overall muscle hypertrophy. However, these and other findings highlighting the dynamic transcriptional response of muscle to contraction, in reality illustrate the inherent difficulty of gaining true physiological meaning from 'snapshots' of data, particularly when studies are performed in the absence of measures of target protein expression and muscle protein turnover. Indeed, it is likely that at least some of the acute transcriptional response to exercise simply reflects a one off response to unaccustomed muscle contraction, which rapidly wanes when further bouts of exercise are performed (Constantin et al., 2013). Furthermore, the response of MAFbx/atrogin-1 mRNA to resistance exercise has been shown to be highly variable across studies (Murton et al., 2008). Nevertheless, the decline in myostatin mRNA expression levels following resistance exercise [Deldicque et al., 2008; Mascher et al., 2008; Hulmi et al., 2009; Dennis et al., 2008; Drummond et al., 2008] provides some level of credence to the suggestion of an elevated myogenic response 24 h post exercise (also because the response appears to be sustained throughout a program of resistance training, Jones et al., 2004), although this has not been universally observed [Jensky et al., 2007].

Interestingly, it has been demonstrated that mRNA expression levels of proteins involved in ubiquitin-proteasome mediated protein degradation vary depending on whether shortening of lengthening muscle contractions are performed in the same individual [Nedergaard et al., 2007]. Specifically, the authors demonstrated increased mRNA levels for proteasome subunit alpha-1, ubiquitin B and ubiquitin C occurred exclusively following eccentric exercise; in contrast, elevations in mRNA levels for Foxo1 and an additional ubiquitin ligase linked to muscle atrophy conditions, MuRF1 [Lecker et al., 2004], were limited to concentric exercise. mRNA levels of MAFbx/atrogin-1 remained at or below basal levels following eccentric and concentric exercise. These observations led the authors to conclude that the disparity between the two modes of exercise were due to the increased drive for muscle remodeling as a consequence of purported myofibrillar damage following eccentric exercise and the increased energy demands of concentric versus eccentric exercise at the same relative workload. In support of the latter suggestion, Foxo1 is known to co-ordinate processes involved in carbohydrate oxidation [Crossland et al., 2008], in addition to acting as a transcription factor to MAFbx/atrogin-1 and MuRF1 [Sandri et al., 2004; Stitt et al., 2004]. The authors proposed that the contradiction of the measured changes in MAFbx/atrogin-1 and MuRF1 mRNA levels to their perceived role in muscle protein breakdown is indicative of MAFbx/atrogin-1 and MuRF1 being instrumental to muscle atrophy and not muscle proteolysis per se. Indeed, the observations that MAFbx/atrogin-1 and MuRF1 protein levels do not necessarily reflect limb protein breakdown in humans [Greenhaff et al., 2008], or the purported regulatory role of MuRF1 in muscle protein synthesis [Baehr et al., 2011] and energy metabolism via modulation of creatine kinase activity [Koyama et al., 2008], provides weight to the authors' assertions. It is perhaps the case that MAFbx and MuRF1 could be ubiquitinating proteins in a signaling manner (i.e. not conjugating ubiquitin via Lys48), rather than to marking them for degradation. This being the case, one could envisage increased MAFbx and MuRF1 activity leading to events that induce atrophy, but not by directly increasing UPS-mediated proteolysis.

It is acknowledged that eccentric exercise training (muscle lengthening whilst developing tension), when performed at high

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