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Redox control of skeletal muscle atrophy

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ABSTRACT

Skeletal muscles comprise the largest organ system in the body and play an essential role in body movement, breathing, and glucose homeostasis. Skeletal muscle is also an important endocrine organ that contributes to the health of numerous body organs. Therefore, maintaining healthy skeletal muscles is important to support overall health of the body. Prolonged periods of muscle inactivity (e.g., bed rest or limb immobilization) or chronic inflammatory diseases (i.e., cancer, kidney failure, etc.) result in skeletal muscle atrophy. An excessive loss of muscle mass is associated with a poor prognosis in several diseases and significant muscle weakness impairs the quality of life. The skeletal muscle atrophy that occurs in response to inflammatory diseases or prolonged inactivity is often associated with both oxidative and nitrosative stress. In this report, we critically review the experimental evidence that provides support for a causative link between oxidants and muscle atrophy. More specifically, this review will debate the sources of oxidant production in skeletal muscle undergoing atrophy as well as provide a detailed discussion on how reactive oxygen species and reactive nitrogen species modulate the signaling pathways that regulate both protein synthesis and protein breakdown.

1. Introduction

Skeletal muscle fiber size is regulated by the balance of protein synthesis and protein breakdown. For example, when the rate of muscle protein breakdown exceeds the pace of protein synthesis, muscle fibers lose protein and atrophy occurs. The loss of muscle contractile protein results in a decreased capacity to generate force (i.e., muscle weakness). Numerous conditions promote skeletal muscle atrophy including chronic inflammatory diseases and prolonged periods of muscle inactivity. Diseases that are often associated with skeletal muscle atrophy include cancer, kidney disease, heart failure, and chronic obstructive pulmonary disease (COPD). Independent of disease, prolonged muscle inactivity (e.g., prolonged bedrest or limb immobilization) also results in muscle atrophy. Regardless of the cause, skeletal muscle atrophy results in muscular weakness and a diminished quality of life [1]. Importantly, excessive loss of muscle mass during disease is also associated with increased morbidity and mortality [2].

The development of a therapeutic intervention to prevent muscle wasting requires an understanding of the cellular signaling pathways that regulate both protein synthesis and proteolysis in muscle. During the past two decades, numerous studies have advanced our knowledge of the cell signaling pathways that regulate muscle size. In this regard, abundant evidence indicates that oxidative stress and/or nitrosative stress, due to increased production of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS), plays an important role in modulating the signaling pathways that regulate both protein synthesis and proteolysis in skeletal muscle. Indeed, it is widely accepted that oxidative stress contributes to skeletal muscle atrophy due to both disease and prolonged muscle inactivity [3–6]. Further, evidence also links nitrosative stress to skeletal muscle atrophy resulting from chronic disease or prolonged muscle disuse [7,8].

This review summarizes our current understanding of the nexus between ROS/RNS and the cell signaling processes leading to skeletal muscle atrophy. We begin with a brief overview of the sources of ROS and RNS production in skeletal muscle. This will be followed by a discussion of the signaling pathways connecting ROS and RNS to increased proteolysis and regulation of protein synthesis. We conclude with a brief discussion of the role that protein oxidation plays in promoting muscle protein breakdown during conditions that produce muscle atrophy.

2. Sources of ROS and RNS in atrophying skeletal muscle

Both oxidative and nitrosative stress often occur in skeletal muscles undergoing atrophy. In this segment we introduce the pathways responsible for ROS and RNS production in skeletal muscle in response to both chronic inflammatory diseases and prolonged muscle inactivity.

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2.1. Sources of ROS and RNS production in skeletal muscle during chronic illness

The loss of skeletal muscle mass due to illness is termed cachexia. Severe inflammatory diseases including cancer, kidney failure, COPD, and heart failure are common causes of cachexia. Inflammation in a remote organ (e.g., lungs of COPD patient) often results in systemic inflammation which is characterized by high levels of circulating cytokines; this is important because systemic inflammation serves as a trigger for both oxidative and nitrosative stress in skeletal muscle [4–6].

2.1.1. Inflammatory disease-induced ROS production in skeletal muscles

Several circulating pro-inflammatory mediators including interleukein-6, tumor necrosis factor-α (TNF), C-reactive protein, and sphingomyelinase are elevated in patients with chronic inflammatory disease [6]. Among these factors, TNF likely plays a key role in increased ROS production in skeletal muscle fibers [6]. The link between circulating TNF and ROS production in skeletal muscle fibers has been investigated extensively. Briefly, evidence indicates that TNF initiates intracellular ROS production by activating the TNF-1 receptor on the sarcolemma; this triggers a cascade of signaling events leading to an increase in superoxide production in the mitochondria (reviewed in [6]). Early events in this biochemical cascade likely involve signaling by one or more sphingomyelinase isoforms leading to the activation of phospholipase A2 which cleaves membrane lipids to release arachidonic acid; this is significant because arachidonic acid is a substrate for ROS-generating enzymes such as lipoxygenases [6,9]. Moreover, activation of phospholipase A2 has been shown to activate NAD(P)H oxidase to generate superoxide and phospholipase A2 can also stimulate superoxide production in the mitochondria [9].

Another potential link between some diseases that promote cachexia and skeletal muscle ROS production stems from increased plasma levels of angiotensin II (Ang II) which occurs in some diseases [10,11]. For example, several chronic diseases (e.g., congestive heart failure and chronic kidney disease) are often accompanied by elevated circulating levels of Ang II. This is significant because infusion of Ang II in rodents results in increased circulating levels of several cytokines including TNF [11]. As discussed previously, TNF can promote ROS production in skeletal muscle fibers. Moreover, Ang II binding to angiotensin I receptors on the sarcolemma can activate NAD(P)H oxidase which also generates superoxide radicals [10–12]. Therefore, it is likely that chronic inflammatory diseases promote both mitochondrial and cytosolic ROS production in skeletal muscles via increases in circulating TNF and/or Ang II.

Finally, emerging evidence indicates that myostatin is a pro-oxidant that can promote increased ROS production in skeletal muscle fibers [13,14]. The mechanisms responsible for this myostatin-mediated ROS production remain a topic of debate but evidence suggests that myostatin induces oxidative stress through a TNF-mediated mechanism [13]. Moreover, it appears that both TNF and ROS are potent inducers of myostatin and require NFκB signaling for myostatin expression [13]. Together, these results suggest myostatin and TNF are components of a feed forward system by which myostatin triggers the generation of the second messenger ROS, mediated by TNF, which in turn, stimulates myostatin expression.

2.1.2. RNS production in skeletal muscles during disease-induced muscle wasting

In addition to the production of ROS, many chronic diseases also promote an increase in the production of nitric oxide (NO). NO is produced in muscle by nitric oxide synthases and the expression of inducible nitric oxide synthase (iNOS) is often increased in skeletal muscle during inflammatory disease-induced muscle wasting [15–17]. Specifically, studies in heart failure, cancer, and COPD have demonstrated that increased circulating cytokines (e.g., TNF) stimulate iNOS expression in skeletal muscles [15–18]. This augmented expression of iNOS leads to increased production of nitric oxide (NO) and consequently protein nitration.

2.2. Sources of ROS and RNS production in skeletal muscles exposed to prolonged inactivity

Similar to chronic diseases, prolonged periods of muscle disuse results in increased ROS and RNS production in skeletal muscles. Research during the past two decades has provided insight into the sources of both ROS and RNS production in skeletal muscles undergoing disuse-induced atrophy. A discussion of the potential sites of ROS production in inactive skeletal muscles follows.

2.2.1. Prolonged skeletal muscle inactivity promotes increased ROS production

The first evidence that prolonged periods of muscle disuse results in increased oxidative stress in limb skeletal muscles was reported over 20 years ago [19] and these original findings have been confirmed by many investigations (reviewed in [3]). However, unlike inflammatory disease-induced muscle wasting, the disuse-induced ROS production in muscles is not associated with systemic inflammation. Although the causes of disuse-induced oxidative stress in skeletal muscle continues to be investigated, evidence suggests that prolonged skeletal muscle inactivity results in increased superoxide production at multiple locations in the cell including NAD(P)H oxidase, xanthine oxidase, and the mitochondria [20–24]. In regard to the relative contributions of each of these sources of ROS production, recent evidence suggests that mitochondria are a major source of ROS production in inactive skeletal muscles [20,21,25]. For example, compared to mitochondria obtained from skeletal muscles of active rodents, mitochondria from muscle exposed to prolonged periods of disuse release significantly more ROS [26,20,24]. Importantly, treatment of animals with a mitochondrial-targeted antioxidant prevents inactivity-induced oxidative stress in skeletal muscles [20,21,24]. Collectively, these observations suggest that mitochondria are a key source of ROS production in inactive skeletal muscles.

2.2.2. The impact of prolonged muscle inactivity on muscle RNS production remains controversial

At present, the question of whether prolonged muscle inactivity results in increased production of NO remains controversial. On one hand, Suzuki et al. reported that prolonged inactivity in limb skeletal muscles (i.e., 14 days of hindlimb suspension) is accompanied with increased NO levels in the inactive muscle [7]. However, unlike cachectic skeletal muscles, iNOS levels do not increase in limb muscles exposed to prolonged inactivity; therefore, increased NO production via iNOS does not occur in skeletal muscles exposed to prolonged inactivity [7]. Rather, Suzuki and colleagues report that muscle inactivity is associated with a dissociation of neuronal NO synthase (nNOS) from the dystroglycan complex and propose that the release of nNOS from the membrane results in nNOS activation and increased production of NO [7]. The finding that muscle disuse results in increased cytosolic nNOS has been confirmed by others [8,27,28]. Nonetheless, it is important to note that there are no published reports documenting higher NO production by non-membrane bound nNOS [29].

In contrast to the Suzuki et al. findings [7], a recent study concludes that 14 days of hindlimb suspension results in a decrease in both muscle nNOS and NO levels [30]. Similarly,