Published in final edited form as:

Curr Opin Clin Nutr Metab Care. 2006 May ; 9(3): 220–224. doi:10.1097/01.mco.0000222103.29009.70.

Angiotensin II as candidate of cardiac cachexia

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Abstract

Purpose of review—Congestive heart failure is increasing in prevalence and represents a major public health problem. The syndrome of advanced heart failure often includes muscle wasting, commonly termed cardiac cachexia, which is a predictor of poor outcome. Mechanisms of cardiac cachexia are poorly understood, but there is recent evidence that increased angiotensin II, interacting with the insulin-like growth factor-1 system, plays an important role.

Recent findings—In animals, angiotensin II produces weight loss through a pressor-independent mechanism, accompanied by decreased levels of circulating and skeletal muscle insulin-like growth factor-1 and increased mRNA levels of the ubiquitin ligases atrogin-1 and Muscle RING finger-1 in skeletal muscle. Reduced insulin-like growth factor-1 action in muscle leads to increased proteolysis, through the ubiquitin-proteasome pathway, and increased apoptosis. These changes are blocked by muscle-specific expression of insulin-like growth factor-1, likely to be via the Akt/mTOR/p70S6K signaling pathway.

Summary—The link between insulin-like growth factor-1, the ubiquitin-proteasome pathway, and angiotensin II effects has widespread clinical implications for the understanding of mechanisms of catabolic conditions. Therapeutic interventions targeting cross-talk mechanisms between angiotensin II and insulin-like growth factor-1 effects could provide new approaches for the treatment of muscle wasting.

Keywords

angiotensin II; atrophy; insulin-like growth factor-1; muscle wasting; ubiquitin-proteasome pathway

Introduction

Skeletal muscle atrophy occurs in various chronic conditions such as uremia, diabetes, aging, cancer, and congestive heart failure [1,2]. In congestive heart failure, neurohumoral excitation includes activation of the renin-angiotensin-aldosterone system, which can also be activated in other catabolic conditions [3]. Muscle wasting in heart failure is often synonymous with advanced degrees of myocardial dysfunction and a poor prognosis. Although the initial events that trigger muscle breakdown may be different in several conditions, the final process that leads to protein degradation may be similar. This review focuses on our current knowledge of the ubiquitin-proteasome pathway and the role of insulin-like growth factor-1 (IGF-1) in angiotensin II induced muscle atrophy.

Ubiquitin-proteasome pathway

Studies of many different models of muscle wasting have indicated that accelerated proteolysis via the ubiquitin-proteasome pathway is the principle cause of muscle atrophy induced in several types of cachexia, such as fasting, metabolic acidosis, disuse, sepsis, and diabetes [4*].

In mammals, the balance between the overall rates of protein synthesis and degradation is precisely controlled at the cellular level. Thus, mammalian cells have multiple proteolytic systems to perform these degradation processes, as well as complex regulatory mechanisms to ensure that the continual proteolysis is highly selective and to prevent excessive breakdown of cell constituents [5*]. The ubiquitin-proteasome pathway catalyses the breakdown of the majority of cell proteins [6]. This continual degradation of cell proteins was first discovered through a classic experiment in the 1940s, using ¹⁵N-labeled amino acids in adult animals [7].

In most cases, protein substrates are marked for degradation by covalent linkage of a chain of ubiquitin molecules to an internal lysine on the substrate [4*]. This process requires at least three enzymes. The ubiquitin-activating enzyme (E1) utilizes adenosine triphosphate to create a highly reactive thiolester form of ubiquitin, and then transfers it to a ubiquitin-carrier protein (E2), of which approximately a dozen are known. The subsequent transfer of the activated ubiquitin to the substrate requires a ubiquitin-protein ligase (E3). The E3 binds the protein substrate, and also the E2 carrying the activated ubiquitin, and transfers the activated ubiquitin from the E2 to the substrate. When a chain containing four or more ubiquitin molecules has been formed on the protein it is then usually degraded rapidly by the proteasome to yield small peptides [4*]. Two of the E3 ligases, atrogin-1 and muscle RING finger-1 (MuRF-1), are especially noteworthy. Both atrogin-1 and MuRF-1 are upregulated with atrophy resulting from disuse [8,9,10**] and atrogin-1 or MuRF-1 knockout mice are resistant to denervation induced muscle atrophy [8].

Heart failure and angiotensin II

Congestive heart failure is a leading cause of cardiovascular mortality and morbidity [11] and is associated with elevated circulating levels of angiotensin II [12] and muscle wasting, which is an important predictor of outcome in patients with this disease [1,13]. In rodents, angiotensin II infusion produced a marked reduction in body weight [14] and a reduction in circulating and skeletal muscle IGF-1. Angiotensin II-induced weight loss, due to both anorexigenic and catabolic effects, as indicated by pair-feeding experiments [15].

Angiotensin II-induced wasting is blocked by an angiotensin II type 1 receptor antagonist [14] and is accompanied by an increase in glucocorticoid levels [15]. Glucocorticoids have been shown to be required for stimulation of the ubiquitin-proteasome pathway in diabetes, fasting, and metabolic acidosis [14–20]. Besides promoting proteolysis in muscle, glucocorticoids also inhibit protein synthesis by decreasing translation of mRNAs encoding muscle proteins and suppressing amino acid entry into muscle. It has also been shown that acute treatment with corticosteroids decreases IGF-1 expression in rat skeletal muscle [21], and IGF-1 gene transfer inhibits glucocorticoid induced muscle atrophy in rats [22*]. It is of note that a glucocorticoid receptor antagonist, Ru486, significantly blocked angiotensin II-induced weight loss in rodents, consistent with a role for glucocorticoids in angiotensin II-induced muscle wasting [23**].

Insulin-like growth factor-1 signaling pathways and hypertrophy

IGF-1 is a major regulator of skeletal muscle hypertrophic responses [24–27]. Thus, muscle-specific over-expression of IGF-1 has been shown to ameliorate the dystrophic phenotype in the MDX mouse (an animal model for Duchenne muscular dystrophy) [28], and has been shown to accelerate muscle regeneration [29].

IGF-1 binding, which can be modulated via the effects of IGF binding proteins, activates the IGF-1 receptor (IGFR), a receptor tyrosine kinase. The IGFR subsequently recruits the insulin receptor substrate (IRS-1), which results in the activation of at least two signaling pathways; the Ras-Raf-MEK-ERK pathway [30,31] and the PI3K-Akt pathway [30]. The Ras-Raf-MEK-ERK pathway is crucial in mitosis-competent cells for cell proliferation and cell survival. In adult skeletal muscle however, the function of the Ras-Raf-MEK-ERK pathway is less clear; some studies have demonstrated that this pathway, downstream of Raf, is actually inactivated during hypertrophy [32], as a result of cross-talk from the PI3K-Akt pathway [32–34]. In contrast, genetic activation of PI3K was shown to be sufficient to induce skeletal muscle hypertrophy [35]. Furthermore, skeletal myotube hypertrophy induced by IGF-1 could be inhibited by a pharmacological inhibitor of PI3K. Therefore, PI3K activity is necessary for IGF-1 to induce hypertrophy, and its activation is sufficient to induce hypertrophy. Expression of an activated form of Akt1 in skeletal muscle cells is sufficient to induce hypertrophy [33,36,37]. Downregulation of the Akt pathway has been observed in skeletal muscle atrophy [20]. Of note, negative regulators of insulin and IGF-1 signaling include phosphatases such as SHIP-2 (SH2-domain-containing inositol phosphatase-2) and PTEN (phosphatase and tensin homologous on chromosome 10). SHIP-2 over-expression blocks hypertrophy in muscle [36,38] and SHIP-2 knockout mice died after birth because of increased insulin sensitivity and hypoglycemia as a result of an increase in Akt2 activity [39]. Similarly, overexpression of PTEN inactivates Akt1 [40] and causes a reduction in cell size [41–43]. Conversely, expression of a dominant-negative mutant form of PTEN in the heart induces cardiac hypertrophy [44].

IGF-1 activation of PI3K-Akt leads to downstream activation of mTOR and p70S6K. Amino acids can also activate mTOR directly, causing a subsequent stimulation of p70S6K activity [45,46], and mTOR appears to have a central function in integrating a variety of growth signals resulting in protein synthesis. Akt phosphorylates mTOR [47], thereby activating it [47,48] and both Akt phosphorylation and mTOR phosphorylation are increased during muscle hypertrophy [49]. Rapamycin, an mTOR inhibitor [50], blocks activation of p70S6K downstream of either activated Akt1 or IGF-1 stimulation [33,36,50]. Treatment with rapamycin decreases hypertrophy [36] and muscle growth [50]. Rapamycin does not however completely block IGF-1-mediated hypertrophy *in vitro*, which might suggest that other pathways downstream of Akt1, but independent of mTOR, play a role in some settings of hypertrophy. Treatment *in vivo* with rapamycin, however, completely blocked compensatory hypertrophy, and inhibited the activation of p70S6K normally observed in Akt/mTOR mediated hypertrophy [38].

Insulin-like growth factor-1, angiotensin II and atrophy

IGF-1 is an important anabolic growth factor for skeletal muscle [51], promoting myoblast proliferation and myogenic differentiation [52,53]. IGF-1 expression is increased during compensatory hypertrophy of muscle [24]. As detailed above, the signaling mechanisms mediating IGF-1-induced hypertrophy are incompletely understood and could include the PI3K/Akt pathway, the downstream mTOR/p70S6K or Akt/GSK3 β pathway [36]. In angiotensin II infused animals, muscle loss was accompanied by depression of circulating and skeletal muscle IGF-1 [14,15]. A reduction in skeletal muscle IGF-1 has also been

reported in rodents with ischemia-induced chronic left-ventricular dysfunction and in patients with chronic congestive heart failure [54,55^{**}]. We had previously failed to correct angiotensin II induced muscle loss by infusing IGF-1 [15]. These findings suggested that autocrine effects of IGF-1 predominated in this model and were consistent with the demonstration that a liver-specific null mutation for IGF-1 failed to retard muscle growth [56]. Overexpression of IGF-1 in skeletal muscle (MLC/migf-1 mice), however, effectively blocked angiotensin II-induced muscle loss, strongly suggesting that depression of skeletal muscle IGF-1 played a causal role in angiotensin II-induced muscle loss [23^{**}]. Interestingly, MLC/migf-1 mice have muscle hypertrophy that is not accompanied by increased Akt phosphorylation, but when these mice are crossed with MDX mice, the resultant MDX:MLC/migf-1 mice have improved muscle mass and function, and a marked increase in Akt phosphorylation in muscle [28]. In addition, MLC/migf-1 mice showed a marked increase in mTOR and p70S6K phosphorylation in muscle [23^{**},57^{**}]. Thus, IGF-1 mediated skeletal muscle hypertrophy is accompanied by increased phosphorylation of mTOR and p70S6K, (but not Akt) *in vivo* [57^{**}].

In angiotensin II infused rodents, there was a reduction in skeletal muscle phospho-Akt that was completely blocked in the MLC/migf-1 mice. Moreover, mTOR and p70S6K phosphorylation was not reduced in MLC/migf-1 mice receiving angiotensin II, but was markedly reduced by angiotensin II in WT mice. These data indicated that IGF-1's ability to prevent angiotensin II-induced muscle loss was likely to be mediated via the Akt/mT OR/ p70S6K pathway [23^{**}].

As noted previously, enhanced protein breakdown, a central event in catabolic loss of muscle proteins, is primarily mediated by the ubiquitin-proteasome pathway [2]. Recently, it has been shown that induction of the ubiquitin-proteasome pathway in atrophying skeletal muscle was accompanied by activation of the forkhead transcription factor (FOXO) [10^{**}]; and increased expression of the ubiquitin-protein ligase atrogin-1/MAFbx [23^{**},55^{**},58^{*}]. We have recently shown that activation of caspase-3, leading to actin cleavage, a critical early event in the protein degradation pathway, also contributes to proteolysis in angiotensin II-infused animals [23^{**},59^{**}]. Intriguingly, overexpression of atrogin-1/MAFbx induces atrophy *in vitro* [60^{*}], whereas muscle atrophy was prevented in animals with targeted deletion of atrogin-1/MAFbx [8]. Of note, IGF-1 has been shown to inhibit starvation and glucocorticoid-induced atrogin-1 expression and atrophy of cultured myotubes via inactivation of FOXOs [55^{**}]. Furthermore, overexpression of constitutively active FOXO enhances activity of the atrogin-1/MAFbx promoter and increases level of atrogin-1/MAFbx mRNA [18]. It has been recently demonstrated that enhanced phosphorylation of mTOR (independent of FOXO) participates in the regulation of atrogin-1/MAFbx expression [18,61^{**}].

Intriguingly, we found that caspase-3 activity is markedly increased in muscle from angiotensin II-infused mice, leading to actin cleavage, increased proteolysis and increased apoptosis. Furthermore, angiotensin II-induced upregulation of atrogin-1 and MuRF-1 mRNA levels in skeletal muscle was partially blunted in the presence of caspase inhibition, which suggested the possible involvement of a caspase-3-dependent mechanism in angiotensin II-mediated upregulation of ubiquitin ligase expression [23^{**}]. Caspase activation and upregulation of ubiquitin ligase expression were prevented by expression of an IGF-1 transgene, consistent with a model wherein the depression of skeletal muscle IGF-1 and of IGF-1 signaling plays the central role, leading to activation of caspase-3 and to increased transcription of ubiquitin ligases and increased proteolysis.

Conclusion

Angiotensin II-induced muscle atrophy is mediated by reduced action of IGF-1 in skeletal muscle resulting from decreased IGF-1 expression and signaling, resulting in stimulation of the ubiquitin-proteasome pathway, activation of caspase-3, and apoptosis. The ability of IGF-1 overexpression to prevent angiotensin II-induced reduction in phospho-Akt, phospho-mTOR, phospho-p70S6K and activation of caspase-3 strongly suggest that angiotensin II reduction in Akt/mTOR/p70S6K signaling plays a pivotal role in stimulation of the ubiquitin-proteasome pathway, increased apoptosis and muscle atrophy. These findings provide a rationale for developing new therapeutic strategies for skeletal muscle wasting conditions.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 330).

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Abbreviations

FOXO	forkhead transcription factor
IGF	insulin-like growth factor
MuRF	muscle RING finger