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Review

Molecular mechanisms and signaling pathways of angiotensin II-induced muscle wasting: Potential therapeutic targets for cardiac cachexia☆

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ABSTRACT

Cachexia is a serious complication of many chronic diseases, such as congestive heart failure (CHF) and chronic kidney disease (CKD). Many factors are involved in the development of cachexia, and there is increasing evidence that angiotensin II (Ang II), the main effector molecule of the renin–angiotensin system (RAS), plays an important role in this process. Patients with advanced CHF or CKD often have increased Ang II levels and cachexia, and angiotensin-converting enzyme (ACE) inhibitor treatment improves weight loss. In rodent models, an increase in systemic Ang II leads to weight loss through increased protein breakdown, reduced protein synthesis in skeletal muscle and decreased appetite. Ang II activates the ubiquitin–proteasome system via generation of reactive oxygen species and via inhibition of the insulin-like growth factor-1 signaling pathway. Furthermore, Ang II inhibits 5′ AMP-activated protein kinase (AMPK) activity and disrupts normal energy balance. Ang II also increases cytokines and circulating hormones such as tumor necrosis factor-α, interleukin-6, serum amyloid-A, glucocorticoids and myostatin, which regulate muscle protein synthesis and degradation. Ang II acts on hypothalamic neurons to regulate orexigenic/anorexigenic neuropeptides, such as neuropeptide-Y, orexin and corticotropin-releasing hormone, leading to reduced appetite. Also, Ang II may regulate skeletal muscle regenerative processes. Several clinical studies have indicated that blockade of Ang II signaling via ACE inhibitors or Ang II type 1 receptor blockers prevents weight loss and improves muscle strength. Thus the RAS is a promising target for the treatment of muscle atrophy in patients with CHF and CKD. This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

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Contents

Abbreviations: Ang II, angiotensin II; AT1R, angiotensin II type 1 receptor; CHF, congestive heart failure; ESRD, end-stage renal disease; ACE, angiotensin-converting enzyme; UPS, ubiquitin proteasome system; ROS, reactive oxygen species; IGF-1, insulin-like growth factor-1; IRS-1, insulin receptor substarte; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated kinase; ERK, extracellular signal-regulted kinase; IL-6, interleukin-6; SAA, serum amyloid A; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; GR, glucocorticoid receptor; AMPK, AMP-activated kinase; AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; Npy, neuropeptide Y; AgRP, agouti-related protein; CRH, corticotropin-releasing hormone; TRH, thyrotropin-releasing hormone; POMC, proopiomelanocortin.

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1. Introduction

Angiotensin II (Ang II), the main effector molecule of the renin–angiotensin system (RAS), has multiple physiological actions including regulation of blood pressure and salt/water balance through a variety of effects on the central nervous system, the adrenal gland, the vasculature and the kidney. Furthermore, the RAS plays an important role in the pathogenesis of all stages of cardiovascular disease, ranging from early endothelial dysfunction to target-organ damage, congestive heart failure (CHF), renal or cerebrovascular disease (Werner et al., 2010). Patients with advanced cardiovascular or renovascular disease, such as CHF or end-stage renal disease (ESRD), often have cachexia, which independently worsens outcome (Tan and Fearon, 2008; Werner et al., 2010). These patients often have increased Ang II levels (Masson et al., 1998; Roig et al., 2000; Anker et al., 2003), and ACE inhibitor treatment improves weight loss in CHF patients (Anker et al., 2003) and AT1 receptor blockade prevents skeletal muscle atrophy in a rat model of CHF (Dalla Libera et al., 2001), suggesting that Ang II could play an important role in the development of cachexia. Interestingly, an ACE inhibitor attenuated weight loss in a mouse model of cancer cachexia (Sanders et al., 2005), which suggests that Ang II signaling may be important not only in patients with CHF and ESRD, but also in cancer cachexia. In this review, we address the relationship between the RAS and skeletal muscle atrophy, the cellular and molecular mechanisms underlying this process, and its physiological and clinical importance.

2. Ang II increases protein degradation

Brink et al. first demonstrated that Ang II infusion in the rat caused a significant loss of body weight through a reduction of food intake and increased proteolysis in skeletal muscle (Brink et al., 1996). These effects were completely prevented by the AT1 receptor blocker losartan but not by the anti-hypertensive drug hydralazine, showing that Ang II causes muscle wasting via an AT1 receptor dependent mechanism independent of blood pressure increase. Ang II infusion causes an increase of protein breakdown and a decrease in IGF-1 signaling, which is the main anabolic pathway in skeletal muscle (Brink et al., 2001). A small component of the muscle wasting may be due to lower levels of protein synthesis, as synthesis rate was lower in Ang II-infused rats, but the difference was not statistically significant (Brink et al., 2001). Ang II-induced protein degradation was prevented by the proteasome inhibitor MG132, but not by lysosomal or calcium-activated protease inhibition, indicating that Ang II induces protein breakdown via the ubiquitin–proteasome system (UPS).

Studies of many different models of muscle wasting have indicated that accelerated proteolysis via the UPS is the principle cause of muscle atrophy induced in several types of cachexia, such as fasting, metabolic acidosis, disuse, sepsis and diabetes (Ventadour and Attaix, 2006). Muscle fiber atrophy in conditions leading to cachexia may be fiber-type specific. Thus, type I fibers are more sensitive to inactivity, microgravity and denervation-induced atrophy, whereas type II fibers are more vulnerable to cancer cachexia, diabetes, CHF and aging (Wang and Pessin, 2013). The UPS degrades the major contractile skeletal muscle proteins and the activation of the UPS is responsible for progression of muscle wasting, whereas the other proteolytic enzymes act upstream (m-calpain, cathepsin L and/or caspase-3) and downstream (tripeptidyl-peptidase II and aminopeptidases) of the UPS for the complete breakdown of the myofibrillar proteins. Proteins that are subject to be broken down are marked for degradation by covalent linkage of a chain of ubiquitin molecules to an internal lysine on the protein and subsequently degraded by the 26S proteasome. This process is regulated by a series of enzymes, E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzyme and E3 ubiquitin ligase. Ubiquitin monomers are activated and linked to E1, transferred to E2, and interact with one of several hundred E3 to be transferred to the substrate protein. The ubiquitin-marked proteins are degraded by the 26S proteasome complex. The 26S proteasome complex is formed by a 20S core catalytic complex and one or two 19S regulatory complexes in charge of substrate recognition. The muscle specific E3 ubiquitin ligases atrogin-1/MAFbx and muscle RING finger-1 (MuRF-1) have been identified as genes strongly upregulated in different atrophy models (Bodine et al., 2001a). Overexpression of atrogin-1/MAFbx in cultured myotubes caused atrophy, whereas denervation-induced muscle atrophy is partially prevented in atrogin-1/MAFbx and MuRF-1 deficient animals (Bodine et al., 2001a). These data show that atrogin-1/MAFbx and MuRF-1 are critical regulators of the UPS and muscle atrophy. However, although Atrogin-1/MAFbx expression has been extensively used as a marker of skeletal muscle atrophy in many studies, it is of note that recent studies showed that such changes do not necessarily reflect alterations in muscle proteolysis per se as previously believed (Attaix and Baracos, 2010). Myosin heavy chain (MHC) (Clarke et al., 2007) and myofibrillar proteins (Cohen et al., 2009) have been identified as substrates of MuRF-1, indicating that MuRF-1 is involved in muscle protein breakdown in atrophying muscle. On the other hand, the only proteins identified so far as a substrate of Atrogin-1/MAFbx is MyoD (Tintignac et al., 2005; Lagirand-Cantaloube et al., 2009) and eukaryotic translation initiation factor subunit F (eIF3-f) (Lagirand-Cantaloube et al., 2008; Csibi et al., 2009, 2010), which regulate muscle differentiation and protein synthesis, respectively. These data suggest that MuRF-1 is associated with muscle proteolysis, whereas Atrogin-1/MAFbx may be more related to protein synthesis. Also, it has been shown that the expression of multiple proteasome components are increased in different atrophy models (fasting, cancer cachexia, diabetes and uremia), including the 20S core complex (Psma1, Psma5, PSmb3 and Psmb4) and the 19S regulatory complex (Psmc4, Psmd8 and Psmd11) (Lecker et al., 2004). In Ang II-induced muscle wasting, expression of atrogin-1/MAFbx and MuRF-1, levels of ubiquitin-conjugated proteins and 20S proteasome activity are robustly increased (Song et al., 2005; Yoshida et al., 2010; Semprun-Prieto et al., 2011). These data indicate that Ang II activates the UPS in skeletal muscle by increasing expression of UPS components and by increasing 20S proteasome activity (Fig. 1).

3. Insulin-like growth factor-1 (IGF-1) and Ang II interaction

Various protective factors are reported to help maintain muscle integrity (Tatsumi, 2010). Among these factors, insulin-like growth factor-I (IGF-1) modulates muscle size via autocrine and paracrine signals by directly stimulating protein anabolism in myofibers

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