Mechanisms of Ageing and Development 129 (2008) 593–601

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Review

Modulation of GH/IGF-1 axis: Potential strategies to counteract sarcopenia in older adults

Silvia Giovannini [a,b,*], Emanuele Marzetti [a,b], Stephen E. Borst [c], Christiaan Leeuwenburgh [a,*]

[a] Department of Aging and Geriatric Research, Division of Biology of Aging, Genomics and Biomarkers Core of The Institute on Aging, University of Florida, Gainesville, USA
[b] Department of Gerontology, Geriatrics and Physiatrics, Catholic University of the Sacred Heart, Rome, Italy
[c] Malcom Randall Veterans Affairs Medical Center, Geriatric Research, Education and Clinical Center (GRECC), Gainesville, FL 32608-1135, USA

ARTICLE INFO

Article history:
Received 4 March 2008
Received in revised form 30 July 2008
Accepted 3 August 2008
Available online 13 August 2008

Keywords:
Aging
Sarcopenia
GH/IGF-1 axis
Angiotensin
ACE-inhibitors

ABSTRACT

Aging is associated with progressive decline of skeletal muscle mass and function. This condition, termed sarcopenia, is associated with several adverse outcomes, including loss of autonomy and mortality. Due to the high prevalence of sarcopenia, a deeper understanding of its pathophysiology and possible remedies represents a high public health priority. Evidence suggests the existence of a relationship between declining growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels and age-related changes in body composition and physical function. Therefore, the age-dependent decline of GH and IGF-1 serum levels may promote frailty by contributing to the loss of muscle mass and strength. Preclinical studies showed that infusion of angiotensin II produced a marked reduction in body weight, accompanied by decreased serum and muscle levels of IGF-1. Conversely, overexpression of muscle-specific isoform of IGF-1 mitigates angiotensin II-induced muscle loss. Moreover, IGF-1 serum levels have been shown to increase following angiotensin converting enzyme inhibitors (ACEIs) treatment. Here we will review the most recent evidence regarding age-related changes of the GH/IGF-1 axis and its modulation by several interventions, including ACEIs which might represent a potential novel strategy to delay the onset and impede the progression of sarcopenia.

1. Introduction

Frailty is a common pathophysiological condition in older adults characterized by diminished reserve capacity and increased risk of disability, institutionalization and mortality. Poor muscle strength is a central feature of frailty, and sarcopenia has been identified as a major modifiable risk factor for this syndrome (Roubenoff, 2000). Multiple factors have been evoked in the etiology of sarcopenia. Among them, atrophy of skeletal muscle fibers secondary to loss of α-motor neurons (Vandervoort, 2002) appears to represent a major causative factor. Other mechanisms are also involved, such as physical inactivity (Szulc et al., 2004), increased levels of pro-inflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-1β, interleukin-6, etc.) (Visser et al., 2002), increased production of free radicals and/or diminished antioxidant defense systems (Fulle et al., 2004), malnutrition (Dreyer and Volpi, 2005), and low anabolic hormone output (e.g., testosterone, growth hormone, etc.) (Szulc et al., 2004). Regarding the latter, attention has been recently focused on the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis, which is regarded as an important regulator of body composition. Notably, local as well as systemic isoforms of IGF-1 have been described. Skeletal muscle expresses at least two distinct splicing variants of IGF-1, namely IGF-1Ea, which is similar to the systemic form, and the mechano growth factor (MGF), which is released in response to physical activity (Yang et al., 1996). These two muscle-derived variants of IGF-1 have different actions, with IGF-1Ea being a potent stimulator of protein synthesis, while MGF promotes satellite cells proliferation.

Serum levels of GH as well as those of its systemic mediators decline with advancing age, and this has been associated with detrimental changes in body composition (i.e., reduction of lean body mass and increased adiposity). Besides the dysfunction of GH/IGF-1 axis, alteration of other humoral factors may be involved in the onset and progression of muscle loss and physical disability at old age. In this regard, angiotensin II has been shown to enhance protein degradation and reduce the autocrine production of IGF-1

* Corresponding authors at: Department of Aging and Geriatric Research, Institute on Aging, Division of Biology of Aging, University of Florida, 210 East Mowry Road, PO Box 112610 Gainesville, FL 32611, USA. Tel.: +1 352 273 5734; fax: +1 352 273 5737.
E-mail addresses: sgiovannini@aging.ufl.edu (S. Giovannini), cleeuwen@aging.ufl.edu (C. Leeuwenburgh).

0047-6374/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.mad.2008.08.001

in rat muscle (Brink et al., 1996, 2001). In contrast, overexpression of muscle-specific IGF-1 (both splicing variants) almost completely prevented angiotensin II-induced muscle loss in mice (Song et al., 2005). Recent evidence suggests that angiotensin converting enzyme inhibitors (ACEIs) may induce positive changes on body composition and physical function in older populations (Onder et al., 2002). It is also documented that ACEIs increase blood flow to muscles (Frisbee and Lombard, 2000), raise skeletal muscle glucose uptake (Kudoh and Matsuki, 2000), and reduce systemic secretion of inflammatory cytokines (Egido and Ruiz-Ortega, 2007). These effects are attributed primarily, but not exclusively, to the inhibition of the renin–angiotensin–aldosterone system.

Here, we will review the most recent findings regarding the modulation of GH/IGF-1 axis by systemic and/or autocrine up-regulation of IGF-1 and ACEIs as potential strategies to counteract the age-associated muscle loss.

2. Biological actions of IGF-1 in skeletal muscle

IGF-1 is perhaps the most important mediator of muscle growth and repair (Goldspink, 2007) and is produced in several ways. In response to GH, the liver produces IGF-1 for systemic release. Skeletal muscle also produces and secretes IGF-1 that possesses autocrine and paracrine actions (Daughaday, 2000). Muscle IGF-1 production may occur in response to GH (Sadowski et al., 2001), testosterone (Bhasin et al., 2001), and muscle overload and stretch (Goldspink et al., 2002). DeVol et al. (1990) were among the first to demonstrate local production of IGF-1 in skeletal muscle. These investigators used a rat model of hypertrophy of the soleus and plantaris muscles following severing of the gastrocnemius tendon. They showed that muscle hypertrophy and IGF-1 production occurred independent of GH, as it was not blunted in hypophesectomized rats that were virtually devoid of circulating GH (DeVol et al., 1990).

Goldspink et al. (2002) have shown that IGF-1 exists in at least two isoforms as a result of alternative splicing of the IGF-1 gene. IGF-1Ea, which is produced in both the liver and muscle, was the first form discovered and it is often referred to as liver-type or systemic IGF-1.

IGF-1Eb (rodent form) and IGF-1Ec (human form) are produced mainly by the muscle and are usually referred to as mechano growth factor (MGF). Unlike MGF, liver-type IGF-1 is glycosylated, which protects it from proteolysis, conferring a relatively long half-life. In muscle, the two forms of IGF-1 are produced in response to different stimuli, have different actions in muscle and probably interact with different receptors. MGF is specifically produced in response to muscle overload, stretch or damage. IGF-1 is both hyperplastic and hypertrophic in skeletal muscle. The hyperplastic effect results in the proliferation of muscle satellite cells, which donate their nuclei to the multinucleated myofiber. The hypertrophic effect results in increased synthesis of contractile proteins by existing myonuclei. In vitro studies with cultured C2C12 mouse myoblasts have provided preliminary evidence that liver-like IGF-1 and MGF may support different aspects of these processes (Yang and Goldspink, 2002). Besides stimulating muscle protein synthesis, IGF-1 also suppresses proteolysis (Ballard and Francis, 1983; Ewton et al., 1987; Hembree et al., 1991). Additionally, IGF-1 may promote the delivery of amino acids and glucose to myocytes (Laager et al., 1993), and stimulate myoblast proliferation and differentiation (Foulstone et al., 2004).

Furthermore, systemic IGF-1 administration increases the rate of skeletal muscle functional recovery after injury (Schertzer and Lynch, 2006), reduces the susceptibility to contraction-induced damage (Schertzer et al., 2006), and improvinges endurance (Gregorevic et al., 2004) and contractile function (Lynch et al., 2001; Gregorevic et al., 2002).

The muscle anabolic properties of autocrine IGF-1 have been confirmed by models of overexpression of locally acting IGF-1 (Barton-Davis et al., 1998, 1999; Coleman et al., 1995; Musaro et al., 2001; Barton et al., 2002). Recently, it has been demonstrated that up-regulation of muscle IGF-1 accelerates the regenerative process in injured skeletal muscle by modulating the inflammatory response and limiting fibrosis (Pelosi et al., 2007). Additionally, muscle IGF-1 may act as a potent regenerative agent, by increasing the recruitment of transplanted bone marrow stem cells into sites of muscle injury (Musaro et al., 2004).

Interestingly, administration of muscle IGF-1 has been recently shown as a promising strategy to improve cardiac function and reduce infarct size after acute myocardial injury (Santini et al., 2007; Carpenter et al., 2008). Mechanisms hypothesized for this effect include the reduction of inflammatory response (e.g., IL-6 and IL-1β) and the severity of cardiomyocyte apoptosis. Furthermore, mice overexpressing muscle IGF-1 are protected against heart failure-induced sarcopenia possibly via inhibition of the ubiquitin-proteasome pathway of protein degradation. (Schulze et al., 2005).

3. Age-related changes in IGF-1 actions

Several studies suggest that IGF-1 is an important modulator of muscle mass, muscle strength and function, not only during development, but also across the entire life span (Ballard and Francis, 1983; Borst and Lowenthal, 1997). In a recent study, Grounds (2002) has concluded that loss of muscle mass occurring with age is mainly a result of atrophy and subsequent reduction in myofiber number (particularly fast-twitch type 2B), whereas impaired muscle regeneration may be only marginally involved. Grounds further hypothesizes that reduction of IGF-1 signaling may play a prominent role in motor neurons loss (Grounds, 2002). In support of this hypothesis, it has been demonstrated that IGF-1 administration has positive effects on neuronal function by preventing apoptotic death, and by stimulating axonal sprouting and repair of damaged axons (Lewis et al., 1993; Festoff et al., 1995; Vergani et al., 1999).

GH is secreted in a pulsatile manner, and pulse amplitude and frequency are markedly reduced with age (Goya et al., 1999). The main actions of GH are to stimulate the synthesis of IGF-1 by the liver for systemic release and to induce local IGF-1 production in skeletal muscle (Fig. 1). Owino et al. (2001) reported that overload- and stretch-dependent MGF production in muscle was impaired in aged mice. A similar phenomenon has been shown by Hameed and coworkers in older human subjects (Hameed et al., 2003). In addition, advanced age is accompanied by impaired signaling through the IGF type 1 receptor, as both receptor density (Martineau et al., 1999) and receptor affinity for IGF-1 (Arvat et al., 2000) are reduced with age.

Aging is also associated with reduced insulin sensitivity which, in turn, may contribute to the impairment of IGF-1 activity. For instance, insulin directly stimulates hepatic IGF-1 production even in the absence of GH, as indicated by the increase of IGF-1 mRNA abundance in primary cultures of hepatocytes exposed to insulin (Boni-Schnetzler et al., 1991). Insulin may also modulate peripheral IGF-1 activity via regulation of IGF-binding proteins (IGFBPs). In particular, insulin reduces IGFBP-1 levels (Powell et al., 1991), which possesses inhibitory effect on IGF-1 by reducing IGF-1-related glucose consumption (Okajima et al., 1993). In addition, insulin may stimulate the production of IGFBP-3 (Nyomba et al., 1997), the main carrier of IGF-1 in serum. It may therefore be hypothesized that amelioration of insulin sensitivity at old age might contribute to restoring IGF-1 systemic levels and function.