Pharmacological perspectives in sarcopenia: a potential role for renin-angiotensin system blockers?

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Summary

Sarcopenia represents a major health problem highly prevalent in elderly and age-related chronic diseases. Current pharmacological strategies available to prevent and reverse sarcopenia are largely unsatisfactory thus raising the need to identify novel targets for pharmacological intervention and possibly more effective and safe drugs. This review highlights the current knowledge of the potential benefits of renin-angiotensin system blockade in sarcopenia and discuss the main mechanisms underlying the effects.

KEY WORDS: sarcopenia; skeletal muscle; angiotensin; angiotensin-converting enzyme inhibitors; angiotensin receptors blockers.

Introduction

Sarcopenia represents a major health problem and a leading cause of disability, morbility and mortality. It currently affects almost 50 million people worldwide, with estimates of growth to 500 million people in the year 2050 (1, 2). Prevalence of sarcopenia increases substantially with age, being one of the main components in the development of frailty. However, it is still unknown whether sarcopenia in elderly is an inevitable consequence of aging or is the result of a combination of different causative factors. Among them, highly prevalent comorbidities in elderly, including chronic obstructive pulmonary disease, diabetes, hypertension and heart failure, most organ failures, and cancer, promote muscle wasting and the occurrence of frailty. Therefore, the identification of effective strategies to prevent and/or treat sarcopenia, has great importance to support healthy ageing and lower the impact of frailty associated with age-related chronic diseases. On the other hand, sarcopenia may also be caused by chronic drug treatment and at the same time it modifies the pharmacokinetic of drugs thereby decreasing their risk to benefit balance (3).

Despite criteria for diagnosing still remain approximate, pathophysiological hallmarks of sarcopenia are better identified (1, 2). It is defined as progressive and generalized impairment in skeletal muscle strength caused by muscle fibre loss and modifications of muscle quality. In particular, there is evidence documenting a preferential decrease of fast twitch (type II) fibres and a relative increase of the slower (type I) ones. These modifications often are associated with alterations in excitation-contraction properties, such as calcium cycling and handling and other dysfunctional events caused by mitochondrial dysfunctions, metabolic disorders, insulin resistance, lipodistrophy and increased tissue fibrosis. Altogether these changes contribute to decline maximal muscle strength, reducing mainly explosive power but also increasing muscle fatigability.

Multiple risk factors may predispose to develop sarcopenia and likely cooperate with each other contributing to determine the severity and the reversibility of the condition (4). They include the age-related increase of insulin resistance and the decline of different hormones (e.g. estrogens, androgens and growth hormone) and vitamin D. Furthermore, muscle detrimental effects are also induced by pro-inflammatory cytokines (e.g. Il-6 and Il-1) that consistently increase with age, especially in the presence of age-related chronic diseases. Other causative factors include physical inactivity and poor diet, which are pivotal determinants of loss of muscle mass and strength regardless of age. Finally, genetic predisposition also plays a role and likely accounts for inter-individual variations and differences of prevalence among ethnic groups.

To date, few mechanisms have been proposed to mediate the onset and the progression of sarcopenia. Among them, the alteration of metabolic homeostasis and the decreased sensitivity to insulin are hypothesized to imbalance protein turnover in the muscle, favoring protein degradation and fibre wasting. Interestingly, a recent hypothesis shifts the attention from muscle fibre to satellite cells, resident precursors in the muscle that, following recruitment after injury, undergo proliferation and differentiation aimed to regenerate the tissue (5). The pool of satellite cells is depleted by ageing and age-related comorbities, thereby declining muscle regeneration capacity and susceptibility to injuries and sarcopenia.

Identification of effective and safe therapeutic strategies in sarcopenia is an open and rather neglected field of investigation. While the stimulation of satellite cells and/or progenitors transplantation still remain a fascinating approach, current pharmacological strategies available to prevent and reverse sarcopenia are largely unsatisfactory in terms of choice, efficacy and occurrence of adverse reactions. Among the pharmacological interventions different drugs are used, with limited clinical efficacy in relieving sarcopenia (6). Recently, experimental and clinical studies have given interesting insights on role of the renin-angiotensin system (RAS) in the skeletal muscle, suggesting a potential benefit of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) in sarcopenia.

In this review, we briefly highlight current knowledge of the physiological role of RAS in skeletal muscle. We then provide an overview of the potential benefits of ACE inhibitors and ARB in sarcopenia; finally, we discuss the main mechanisms underlying the effects.

RAS in skeletal muscle

In mammals, the endocrine RAS plays a fundamental role in circulatory homeostasis by regulation of blood pressure, fluid and salt balance. Circulating renin is a protease that catalyzes the conversion of hepatic angiotensinogen to angiotensin I, a decapeptide. This is further converted into angiotensin II (Ang II), an octapeptide, by ACE, an endothelial peptidase primarily found within the pulmonary bed and the lung. Ang II is the main effector of RAS that through interaction with specific receptors, particularly its type 1 receptor (AT1R), causes direct vasoconstriction as well as salt and water retention as a consequence of adrenal aldosterone release. Beyond ACE, evidence indicates that a different enzyme, ACE2 negatively modulates the activated RAS by cleaving Ang II to the heptapeptide Ang (1-7). The latter acts through the type 2 receptor (AT2R) and Mas receptor and counterbalances at least part of cardiovascular effects of Ang II by opposing many of the actions mediated by AT1R activation (7-9). Furthermore, ACE converts a different peptide, bradykinin, which exerts a potent vasodilatory effect via activation of bradykinin type-1 and 2 receptors (BK1R, and BK2R, respectively). At tissue and cellular level, function of RAS may be further complex due to the interplay with local or tissue-based RAS. The latter integrates or complements systemic Ang II and exerts paracrine and autocrine functions mostly related to tissue growth and injury responses.

Recent evidences have focused the attention on the physiological role of RAS on skeletal muscle, a target organ largely ignored for Ang II effects. Regulation of local perfusion arising from systemic Ang II is fundamental to regulate metabolic activity and function of skeletal muscle. In addition to this, recent experimental studies (10, 11) document supplementary effects induced by Ang II and downstream receptors mostly related to tissue trophysm and regenerative capacity. Indeed, in animal models the increase of Ang II levels proved to induce skeletal fibre wasting through enhanced protein degradation and apoptosis as well as decreased protein synthesis. Part of these detrimental effects of Ang II are mediated directly by AT1R expressed at skeletal muscle level. Moreover, indirect and negative effects are also provided by intermediate molecules (e.g. cytokines and glucocorticoids), which are released from different sources upon increased Ang II levels. In line with the detrimental effects of RAS activation observed in animal models, patients with cachexia and characterized by extensive muscle loss, also display elevated levels of circulating Ang II (12).

Different studies in humans have demonstrated that reduced expression of ACE because of a genetic polymorphism is associated with greater muscle anabolic response and improved skeletal muscle performance after training (13). It has been suggested that part of the association of ACE genotype with performance phenotype is mediated by modulation of kinin levels and kinin activity at BK2R. However, a beneficial role on muscle trophysm induced by the decrease of Ang II levels and the reduction of AT1R activation may also be hypothesized to concur to the enhanced muscle performance.

Despite further studies are necessary, together these evidence concur to identify RAS and downstream receptors as important regulatory axis in skeletal muscle physiology. The negative effects provided by ANGII/AT1R system represent a basis for a pharmacological approach to RAS blockade potentially useful in sarcopenia.

Effects of RAS blockade in sarcopenia

Different observational data suggest that in cardiovascular patients ACE inhibitors and ARB may improve the decline of muscle performance and reduce the occurrence of frailty (12, 14, 15). Because both classes of drugs share the capacity to decrease the bioavailability and/or the biological activity of Ang II, these evidence led to consider the possibility that reduced levels of Ang II or RAS blockade may slow-down muscle wasting with potential implication for therapy. Interestingly, one of the study performed in cardiovascular patients treated with ACE inhibitors and ARB has demonstrated that the enhanced muscle performance is associated with a key molecular modification of myosin heavy chain, one of the sarcomeric protein in skeletal muscle (16). In fact, while the fast oxidative and glycolytic proteins (MHC2B and 2A) are prominent in the sarcopenic patients, after drug administration they decline and appear to be shifted toward the slow, more fatigue-resistant isoform (MHC1). These results corroborate the concept that RAS inhibition may directly ameliorate the function of skeletal muscle counterbalancing some of the biochemical and structural changes occurring in sarcopenia. In line with data observed in cardiovascular patients, in a rat model of heart failure associated with muscle atrophy and increased fatigability, protective effects of AT1R blockers are also documented and further proved to reverse most of the molecular markers of skeletal muscle wasting (17).

Despite the mechanisms of action of RAS blockade are still controversial, one of the hypothesis is that the benefit on cardiac output and that on hemodynamic parameters could promote skeletal muscle blood supply with positive consequences on muscle metabolism and function. Moreover, ACE inhibitors are also known to improve endothelial function, enhance muscle glucose uptake, increase potassium levels and modulate other hormonal systems including insuline-like growth factor-1, all of which could contribute to improve skeletal muscle function. Finally, a direct trophic effect of RAS blockade in skeletal muscle is supported by different studies on animal models, which provide the opportunity to evaluate the efficacy of RAS blockade on sarcopenia in the absence of cardiovascular diseases. In the setting of muscle atrophy induced by aging (18) or myopathic states (19), ARB
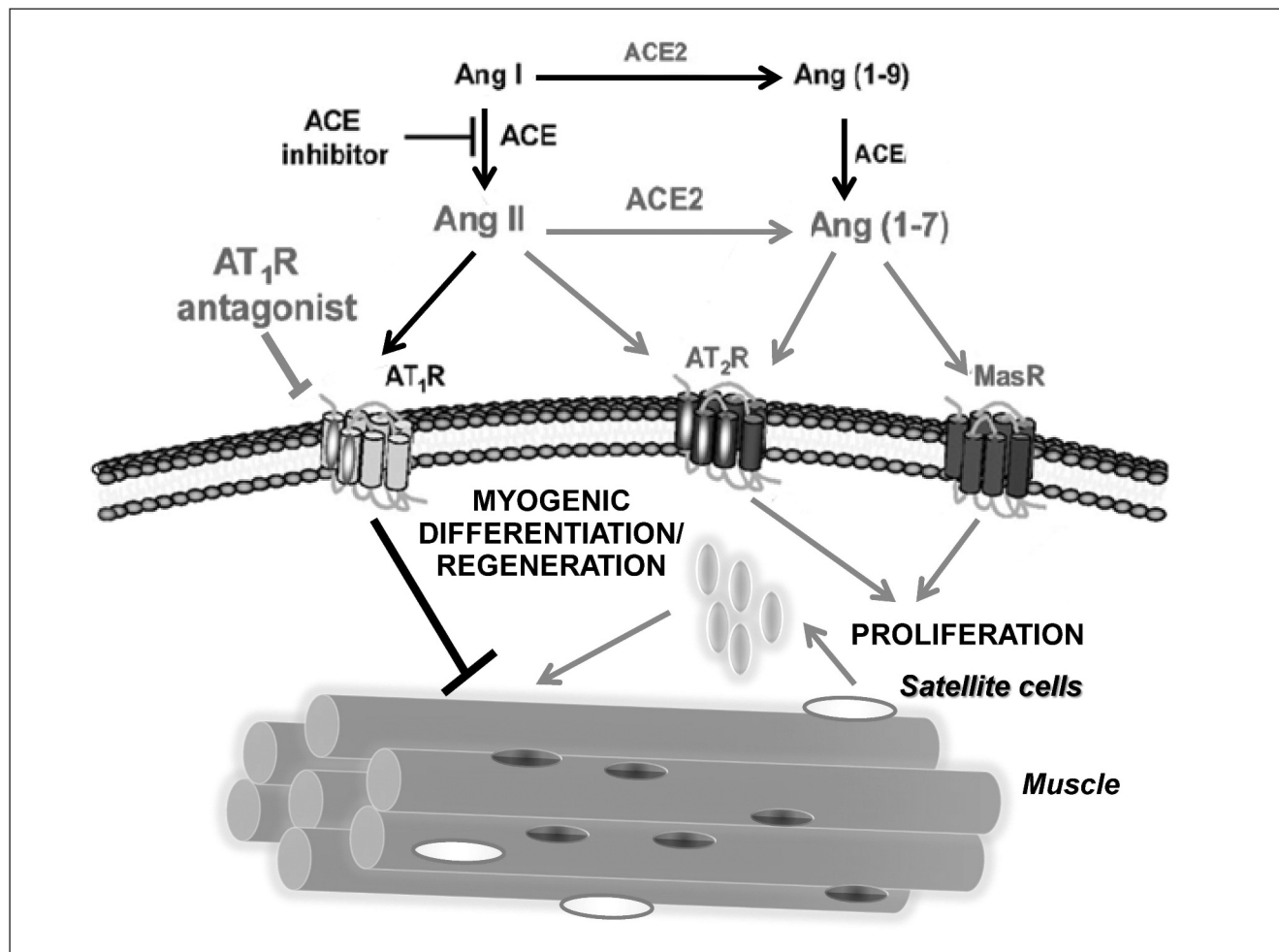
Figure 1 - Schematic representation of RAS axis and of the effect on skeletal muscle.

resulted to be protective against muscle wasting and attenuated failure of muscle regeneration.

Following on from these data, a small randomised controlled trial evaluated the effect of ACE inhibitors on physical function in geriatric patients with impairment of daily activities (20). The intervention group achieved a consistent improvement of muscle performance equivalent to that reported after six months of exercise training. Larger clinical studies are necessary to verify and extend these results.

Recently, a novel mechanism of action for ACE inhibitors and ARB on skeletal muscle has been postulated and partially verified in animal models. The attention was focused on muscle satellite cells as main target of RAS activation or blockade (Figure 1). In these studies Ang II/AT1R axis resulted to reduce satellite cell migration, differentiation and growth (10, 11, 21), fundamental requisites of satellite cells aimed to sustain muscle regeneration after injuries and fibre wasting. Blockade of RAS resulted to protect the pool of satellite cells promoting muscle regeneration and function improvement. Of note, because of AT1R blockade, part of the observed effects may derive from a local shift of Ang II towards muscle AT2R, whose activity is expected to counterbalance that of AT1R activation (Figure 1). Moreover, in the presence of ACE inhibitors Ang II is preferentially degraded by ACE2 that through activation of Ang (1-7)/Mas receptor axis shares a pharmacodynamic profile similar to that of AT2R activation and opposes many of the ac-

tions mediated by AT1R (7). Accordingly, in the mouse Ang (1-7) proved to promote muscle regeneration by activating satellite cell growth and differentiation (22, 23). Whether similar mechanisms occur in humans or in human cells after RAS blockade are presently unknown and represent an important issue to be addressed.

Summary and conclusion

Accumulating evidence have identified RAS as an important regulator of the skeletal muscle, being involved in physiological functions including perfusion, trophism and regeneration capacity. Parallel studies have documented the potential benefits of RAS blockade in different pathologic conditions including sarcopenia and uncovered a positive modulatory role exerted by Ang (1-7) peptide that would activate the "good arm" of RAS.

Despite the progresses made, numerous key questions on the benefits of RAS blockade in sarcopenia still remain unanswered and deserve thorough investigations both in the experimental and clinical setting. If the role of Ang (1-7) in muscle wasting would be confirmed, the peptide and its downstream receptors (AT2R and MAS receptor) might represent novel targets of the RAS axis useful to preserve the pool of satellite cell inside the skeletal muscle and their re-

generative potential in sarcopenia or after muscle injuries. In this context, the identification of selective and stable agonists for Mas receptors would be a valuable achievement as well as the use of selective agonists for AT2R, which are currently the object of researches mainly restricted to the cardiovascular field (24).

Acknowledgements

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