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A REVIEW ON THE ROLE OF ANGIOTENSIN II IN THE SKELETAL MUSCLE HYPERTROPHY AND MUSCLE STRENGTH

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ABSTRACT

Angiotensin II (ANG II) is intensely involved in the hypertrophy of cardiac muscle cells. However, a potential role of ANG II in skeletal muscle hypertrophy has not been widely studied. The objective of the present review is to highlight the molecular mechanisms (if any) behind the role of ANG II in the regulation of the skeletal muscle growth. The available data (however limited) demonstrate that ANG II is necessary for an optimal overload-induced skeletal muscle hypertrophy. Although the exact mechanisms by which ANG II mediates skeletal muscle growth under conditions of overload remain unclear, these effects may be partly mediated by the type 1 receptor (AT1). Moreover, ANG II may influence hypertrophy via its interaction with the insulin-like growth factor I (IGF 1). Furthermore, it appears that circulating ACE (Angiotensin Converting Enzyme) activity is directly associated with human muscle strength. These findings support the assertion that ANG II is likely to act as a growth factor in human skeletal muscle. Identifying the optimal local concentration of ANG II needed to contribute to measurable skeletal muscle hypertrophy is of great importance. Discovering how ANG II may influence muscle hypertrophy/atrophy may lead to the development of new pharmacological interventions designed to increase muscle mass in cases when resistance training cannot be prescribed. Furthermore, finding alternative therapies to increase/preserve muscle mass would have a major impact on geriatric medicine, rehabilitation and sports science.

Keywords: *Angiotensin II, muscle hypertrophy, angiotensin converting enzyme, muscle strength, IGF-1, muscle atrophy.*

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İSKELET KASI HİPERTROFİSİ VE KAS GÜCÜNDE ANJİYOTENSİN II'NİN POTANSİYEL ROLÜ ÜZERİNE BİR DERLEME

ÖZET

Kalp kası hücrelerinin hipertrofisinde anjiyotensin II (ANG II), son derece etkili role sahiptir. Bununla birlikte, iskelet kası hipertrofisinde ANG II'nin potansiyel rolü geniş çapta araştırılmamıştır. Bu derlemenin amacı, iskelet kası büyümesinin düzenlenmesinde ANG II'nin rolünün arkasındaki, eğer varsa, moleküler mekanizmaları vurgulamaktır. Mevcut veriler (sınırlı olmakla birlikte), optimal aşırı yüklenmeye bağlı iskelet kası hipertrofisi için ANG II'nin gerekli olduğunu göstermektedir. ANG II'nin aşırı yük koşulları altında iskelet kası büyümesine aracılık ettiği kesin mekanizmalar belirsiz kalsa da, bu etkilere kısmen tip 1 reseptörü (AT1) aracılık edebilir. Ayrıca ANG II, insülin benzeri büyüme faktörü I (IGF 1) ile etkileşimi yoluyla hipertrofiyi etkileyebilir. Ayrıca, dolaşımdaki ACE (Anjiyotensin Dönüştürücü Enzim) aktivitesinin doğrudan insan kas gücü ile ilişkili olduğu görülmektedir. Bu bulgular, ANG II'nin insan iskelet kasında büyüme faktörü olarak rol alabileceği iddiasını desteklemektedir. Ölçülebilir iskelet kası hipertrofisine katkıda bulunmak için gerekli olan optimal lokal ANG II konsantrasyonunun belirlenmesi büyük önem taşımaktadır. ANG II'nin kas hipertrofisini / atrofisini nasıl etkileyebileceğini keşfetmek, direnç egzersizlerinin yapılamadığı durumlarda kas kütlesini artırmak için yeni farmakolojik ajanların geliştirilmesine yol açabilir. Ayrıca, kas kütlesini artırmak / korumak için alternatif tedaviler bulmak, geriatrik tıp, rehabilitasyon ve spor bilimi üzerinde büyük bir etkiye sahip olacaktır.

Anahtar kelimeler: Anjiyotensin II, kas hipertrofisi, anjiyotensin dönüştürücü enzim, kas gücü, IGF-1, kas atrofisi.

INTRODUCTION

Muscle atrophy is a frequent symptom encountered in various disorders such as rheumatoid arthritis, osteoarthritis, vascular disease, type II diabetes and osteoporosis.[1] In a mature individual, a growth in muscle mass only occurs when the muscle is loaded sufficiently to cause a shift in the myofibrillar protein balance. The regulation of the amount of muscle tissue is determined by the balance between the rates of protein synthesis and degradation.[2]

Skeletal muscle is a tissue with a plasticity that rapidly adapts to its mechanical environment.[3] An increase of the load across a muscle, such as strength exercise or heavy work, results in a compensatory increase in muscle size and strength. This increase in muscle size occurs largely from the growth of existing cells (hypertrophy) rather than an increase in cell number (hyperplasia).[4] Mechanical loading also results in strong adaptive responses in various other tissues including bones and tendons.[5] The main benefit of such adaptive responses is the protection it offers to these tissues against future injury. Conversely, muscle atrophy occurs with the introduction of catabolic stimuli including dietary protein withdrawal and mechanical unloading. Furthermore, muscle atrophy is also common during periods of illness or injury when an individual's physical activity is drastically decreased.[6,7] The exact molecular mechanisms behind the ability of skeletal muscle to hypertrophy in response to load are the focus of this review. Precisely, we will emphasize on the possible role of angiotensin II (ANG II) in skeletal muscle hypertrophy and muscle strength.

In addition, it has been demonstrated that bigger and stronger skeletal muscles improve both the quality and the length of life.[8] Currently, resistance training is the only intervention to increase muscle mass that can be implemented on a population-wide basis. Unfortunately, despite its well proven, wide-ranging benefits, resistance training is still under-prescribed by specialists and is practiced with consistency only by a small minority of individuals.[9,10] However, there are certain circumstances such as injury, illness, bed rest, limited accessibility to facilities, social constraints that may prevent individuals to engage in resistance training. Therefore, finding alternative therapies to increase or preserve muscle mass would have a major impact on population health and well-being. Given this context, the main objective of the present review is to highlight the molecular mechanism of ANG II and its role in regulating load-induced skeletal muscle hypertrophy. The role of ANG II in muscle hypertrophy has not been widely studied and therefore might be exploited for developing new interventions designed to increase muscle mass where resistance training cannot be prescribed.

ANG II is a major vasoconstrictor peptide and it is known to induce various diseases, such as hypertension, cardiac hypertrophy, and renal dysfunction.[11] Recently, it has become known that ANG II may induce skeletal muscle protein breakdown and muscle atrophy via the ubiquitin ligases: atrogin-1 and muscle RING-finger protein-1 (MuRF-1).[12] Furthermore, it has been also shown that administering an angiotensin-converting enzyme (ACE) inhibitor, a blocker of ANG II production,

also suppresses ANG II induced muscle atrophy.[13] Also, the literature shows that ACE inhibitors can attenuate sarcopenia, the age-related loss of muscle mass and function.[14] These findings suggest that the ANG II pathway is important for muscle atrophy, and, furthermore, imply that inhibiting this pathway could prevent sarcopenia.

The Role of Angiotensin II in Skeletal Muscle Hypertrophy

Skeletal muscle adaptions after resistance training have been widely studied both in humans and animal models.[15-16] The main advantage of using animal models comes from the rapid and extensive muscle hypertrophy that can be induced.[17]

As mentioned, the mechanisms leading to skeletal muscle hypertrophy in response to mechanical overload are still unclear, although it is well established that input from both mechanical and hormonal stimuli is necessary for optimal skeletal muscle cell hypertrophy. The role of ANG II in skeletal muscle hypertrophy or muscle strength has hardly been studied in the literature.

However, it is well-known ANG II is strongly involved in overload-induced hypertrophy of cardiac muscle cells. The main argument regarding the role of ANG II in cardiac muscle hypertrophy remains whether ANG II acts on the muscle cells in a paracrine or in an endocrine manner. On one hand, it has been shown that ANG II appears to promote overload-induced cardiac hypertrophy primarily in a paracrine fashion. Using an in vitro model of stretch-induced cardiac hypertrophy, it has been demonstrated that mechanical stretch causes release of ANG II from cardiac myocytes and that ANG II acts as an initial mediator of the stretch-induced hypertrophic response.[18] These findings not only provide direct evidence for the paracrine mechanism in load-induced growth of cardiac muscle cells, but also describe a pathophysiological role of the cardiac renin-angiotensin system.[18] In addition, animal models of overload-induced cardiac hypertrophy demonstrated an upregulated gene expression of RAS components that include renin, angiotensinogen, ACE mRNA amount, ACE activity, intracellular renin and ANG II peptide contents.[19,20] In all of these animal models, ACE activities were not increased in the plasma, suggesting that ANG II acts in a paracrine fashion during cardiac muscle hypertrophy.[21]

Furthermore, the results of the studies in which an ACE inhibitor (e.g. perindopril) was administered during cardiac overload showed that this inhibitor prevented the increase of the cardiac tissue ACE activity and also prevented any significant cardiac hypertrophy.[21] Once more, these results were obtained independently of blood pressure changes, suggesting that the ACE inhibitor did not influence the systemic ANG II.[21] Moreover, in another study, a 15–20% left ventricular hypertrophy was induced by 1 week of systemic ANG II infusion in rats. Similar to the before mentioned data, the reported results of this study showed no significant changes in the blood pressure of the rats.[22]

ANG II seems to act directly on the heart to promote cardiac hypertrophy. The exact mechanism through which ANG II influences cardiac hypertrophy is still unclear, however, some theories suggest that this effect is probably mediated through the ANG II type 1 (AT1) receptor, since studies that used the intervention with AT1 receptor antagonists prevented ANG II-induced cardiac hypertrophy in various animal models.[22,23]

Interestingly, it has been demonstrated that ANG II can induce smooth muscle hypertrophy in a fashion similar to that seen in cardiac muscle.[24] The available data found in the literature shows that the administration of ANG II to cultured smooth muscle cells results in increases in smooth muscle α-actin expression, protein synthesis, and cell hypertrophy.[25,26] Furthermore, increased levels of ACE expression have been observed in smooth muscle cells during vascular repair in humans.[27] In addition, when ACE inhibitors or AT1 receptor blockers are administered to rats, a reduced smooth muscle cell growth in response to injury has been found.[27]

Therefore, it can be safely stated that ANG II plays a significant role in cardiac hypertrophy and smooth muscle growth, particularly under conditions of overload.[20,21] Thus, it may be speculated that ANG II could also mediate overload-induced skeletal muscle hypertrophy through the same mechanisms that were described above.

In the present review, we analyzed the limited available literature to see if ANG II may mediate overload-induced skeletal muscle hypertrophy and to clarify the molecular mechanisms that lay behind this insufficiently-studied connection. The most relevant studies on this topic which have been analyzed in the present paper can also be seen in Table. Thus, one of the main reports that investigated the role of ANG II in striated muscle enlargement demonstrated that using ACE inhibition to partially block ANG II production significantly attenuated overload-induced skeletal muscle hypertrophy.[28] Interestingly, the reported results showed that the ANG II effect was

Table. The limited available literature categorized according to the type of muscle tissue they study

Studies on the effect of ANG II on cardiac muscle hypertrophy	Studies on the effect of ANG II on smooth muscle hypertrophy	Studies on the effect of ANG II on skeletal muscle hypertrophy/atrophy	Studies on the effect of ANG II on skeletal muscle strength
Baker *et al.* 1990	Geisterfer *et al.* 1988	Susic *et al.* 1996	Danser *et al.* 1995
Dostal *et al.* 1992	Ohishi *et al.* 1997	Van Kats *et al.* 1997	Geisterfer *et al.* 1998
Sadoshima *et al.* 1993	Pratt *et al.* 1999	Gordon *et al.* 2001	Hopkinson *et al.* 2004
Chiba *et al.* 1994	Hautmann *et al.* 1999		
Zhang *et al.* 1995			

significantly different between slow twitch muscle and fast twitch muscle fibers. Therefore, it is important that the observed significant effect was greater in the slow-twitch soleus muscle compared to the fast-twitch plantaris muscle.[28] Furthermore, the same authors reported that they were able to rescue 71% of the lost hypertrophy in the right soleus muscles of ACE-inhibited animals with a local treatment with exogenous ANG II in a continuous fashion throughout the loading period. In addition, similar to the cardiac and smooth muscles. The conclusion of the study states that the effect of ANG II in overload-induced skeletal muscle hypertrophy may be at least partly mediated via the AT1 receptor, as overload-induced soleus hypertrophy was attenuated by AT1 receptor blockade regardless of ANG II administration.[28]

Similarly growth of the cardiac and smooth muscle hypertrophy, arises an uncertainty: is the observed significant effect of ANG II levels on skeletal muscle hypertrophy explained by the local increase of the ANG II, or are the systemic levels of ANG II responsible for the observed differences in striated muscle hypertrophy. The authors of the previously-mentioned study pointed out that it cannot be conclusively determined from the results of their investigation. They based their conclusion on the fact that the soleus was only sensitive to locally elevated levels of exogenous ANG II during overloading, because the non-perfused contralateral overloaded soleus was not affected in the same group of animals.[28] However, probably the exogenous ANG II did indeed enter the systemic circulation, given that heart muscle atrophy was observed in the ACE inhibitor treatment but also in the local ANG II perfusion experiment. It has been proven in the literature that is hardly possible in skeletal muscle hypertrophy- induced animal models, to prevent ANG II to become systemic even if it is administered locally.[29] For example, one study reported significant cardiac hypertrophy even if ANG II was administered subcutaneously via osmotic pumps.[29]

As such, an extrapolation of the effects of local skeletal muscle administration of ANG II for the human subjects remains problematic due to the adverse effects of cardiac muscle hypertrophy observed in animal models. One possible explanation on why local ANG II administration in these skeletal muscle hypertrophy-induced animal models remains unachievable may be the fact that binding and accumulation of systemic ANG II are much higher in cardiac muscle compared to any skeletal muscle.[30] Further research is needed to determine if an optimal local concentration of ANG II exists, in order to contribute to a measurable skeletal muscle hypertrophy. It is also essential to avoid the entrance of ANG II in the systemic circulation in order prevent an unwanted heart hypertrophy.

To conclude, the present section of our review shows that ANG II is necessary for optimal overload-induced skeletal muscle hypertrophy. Although, this effect may be partly mediated by the AT1 receptor, the exact mechanism by which ANG II influences skeletal muscle hypertrophy under conditions of overload remains unclear. Furthermore, it also remains unclear if systemic or local levels of ANG II are the origin of this effect on muscle hypertrophy. The available data indicates the existence of a complex RAS involvement in the skeletal muscle hypertrophy and muscle strength. The exact molecular mechanism behind this observed effect is an exciting topic for further investigation and it will be the main focus of the next section of our review. Also, given that a very significant percentage of patients with a tendency towards muscle atrophy are also the recipients of ANG II synthesis blockers or angiotensin receptor blockers (ANG II is used in the treatment of high blood pressure) the relationship between angiotensin metabolism and muscle health should be subjected to much more scrutiny than before.

The Connection Between Angiotensin II, Insulin-like Growth Factor I (IGF-I) and Muscle Hypertrophy/strength

The first mechanism found in the literature through which ANG II may influence hypertrophy refers to its connection with insulin-like growth factor I. Insulin-like growth factor I (IGF-I) is an endocrine and paracrine growth factor that has multiple effects, including stimulation of cell growth and differentiation, erythropoiesis, chemotaxis, anabolism and prevention of muscle atrophy.[31] Furthermore, in skeletal muscle, IGF-I can increase the absorption of glucose and amino acids, enhance protein synthesis and suppress protein degradation.[32] Moreover, studies have shown that IGF-I stimulates mitogenesis in cultured skeletal muscle cells and may induce myoblast differentiation.[33]

Regarding the connection with ANG II, it has been recently found that rats which received ANG II presented a low level of circulating IGF-I. Furthermore, in the same study the observed low levels of IGF-I were accompanied by a significant weight loss.[34] Interestingly, studies have shown that these responses are mediated by the AT1 receptor, but are independent of pressor responses to ANG II. For example, in one study on the ANG II- IGF 1 connection, the obtained increases in ANG II levels were found to be similar to increases observed in patients with congestive heart failure (CHF).[35]

Early on, this connection was studied especially in the animal models. For example, in an animal study on muscle wasting in rats with chronic renal failure, the results showed that muscle wasting is caused by increased protein degradation via activation of the ubiquitin-proteasome system.[36] Although, the mechanisms of chronic renal failure are complex, IGF-I levels were also found to be extremely low in this population of rats.[37] Furthermore, as IGF-I influences both protein synthesis and degradation in muscle tissue, some authors have speculated that a low circulating IGF-I level could be responsible for increased muscle wasting when ANG II levels are high. Therefore, this led various researchers to measure muscle hypertrophy or muscle wasting in response to ANG II and IGF-I levels.

Consequently, the studies that examined how the levels of ANG II and IGF-I may influence the level of muscle hypertrophy/atrophy reported an increase in muscle protein breakdown in response to the treatment with ANG II, which could possibly contribute to weight loss. Regarding the role of IGF-I in the reported increase in muscle protein breakdown, it has been speculated that the mechanism for this proteolytic response (the breakdown of protein) could be related to changes in the IGF-I system. However, in the previously mentioned studies, correcting the level of circulating IGF-I did not lead to normal skeletal muscle hypertrophy/atrophy. On the other hand, the authors reported some evidence for impairment of the autocrine IGF-I system in skeletal muscle, including significantly reduced levels of expression of IGF-I. In addition, they concluded that their results suggest that ANG II causes a loss in skeletal muscle mass by enhancing protein degradation probably via its inhibitory effect on the autocrine IGF-I system.[38]

These findings need further investigations on the grounds that it could lead us to a better understanding of the mechanisms of various human diseases, specifically the molecular mechanisms behind muscle hypertrophy/atrophy in conditions such as congestive heart failure and chronic renal failure in which the RAS is activated.

Another mechanism analyzed in the present review refers to the angiotensin converting enzyme (ACE) and its connection with muscle strength. Considering that muscle size explains ~50 % of the inter-individual variability in maximum strength in the untrained state[39] it is important to also analyze muscle strength and its connection with ANG II. It is well established that muscle size is associated with isometric and isoinertial strength.[40,41] Therefore, a better understanding of the how specific physiological adaptations contribute to the individual improvements in isometric, isoinertial and explosive strength and its connection with ANG II may lead to improved physical performance in athletic groups, a reduced risk of falling in older populations or health improvements in at risk populations suffering from various conditions.

The benefits of strength training are well documented and it has been demonstrated that muscle strength is protective against most of the neuropsychiatric disorders such as dementia, Parkinson's disease, anxiety, depression, autism, schizophrenia or substance abuse disorder.[42-46] Furthermore, a cohort study of 8,762 men aged 20 to 80 years showed that maximum force is independently and inversely associated with all-cause mortality.[46] Therefore, studying and elucidating the molecular mechanism behind skeletal muscle strength, not only behind muscle hypertrophy, is of significant importance and should be the focus of future research.

Therefore, it has been demonstrated that ACE may modulate tissue growth processes; especially it is well documented that ACE regulates cardiac muscle hypertrophy.[47] However, despite the importance of studying the molecular mechanism behind strength gains, few studies have evaluated directly the role of ACE in the regulation of skeletal muscle strength in humans. However, a study on 71 subjects who died of noncardiac disorders have demonstrated that the deletion (D), rather than the insertion (I), variant of the human angiotensin-converting enzyme (ACE) genotype is an important factor in the hypertrophic response of cardiac muscle to exercise.[48] Furthermore, the authors of the mentioned study also speculated that this genotype might explain the observed individual variations in skeletal muscle strength and hypertrophic response to functional overload.[48] Furthermore, in a follow-up study, Hopkinson and colleagues recently reported the same association. The results they reported showed that the deletion allele was associated with greater quadriceps strength independent of confounding factors, among untrained patients with chronic lung disease.[49] However, neither of the previously mentioned articles

could demonstrate this association among healthy untrained individuals. Therefore, the authors of these studies suggested that these findings should not be extrapolated to the general, healthy population.

This observed effect of ACE on muscle strength may be mediated through alterations in skeletal muscle fiber type. This hypothesis states that the ACE-I allele may be associated with increased slow-twitch fiber, which is more efficient than fast-twitch fiber in low-velocity contraction. This effect was investigated in a study with a sample of 41 untrained individuals.[50] The reported results of this investigation showed that ACE-II genotype subjects had significantly higher percentages of type I fibers and lower percentages of type II fibers than ACE-DD subjects. The type I fibers are known to produce greater force per unit of cross-sectional area compared to type II fibers.

Another explanation of the effect of ACE on muscle strength suggests that any action of ACE via ANG II on muscle strength may occur via neural activations. Therefore, ACE may also influence muscle strength through the degradation of kinins. It is well known that skeletal muscle contains a complete kallikrein–kinin system, which can liberate kinins locally and dispatch functional bradykinin B2 receptors. Therefore, as these polypeptides can inhibit growth processes, the elevated circulating ACE may also influence muscle strength via this alternative neuronal route.

In the conclusion of our last section, the available data suggests that circulating ACE activity is associated directly with human muscle strength. These findings support the assertion that we described in the present review; specifically that ANG II is likely to act as a growth factor in human skeletal muscle.

The importance of this present work comes from reviewing the limited available data regarding the influence of ANG II on skeletal muscle hypertrophy and highlighting the importance of future investigations in this yet unconcluded research area. These preliminary findings, although still contradictory, call for further examinations for a greater understanding of the role of ACE and ANG II in the regulation of skeletal muscle hypertrophy and strength. Furthermore, future studies should also focus their attention on the possibility that ACE genotype individuals may respond better to resistance training. Uncovering genetic contributions to muscle performance and its related traits, muscle strength in our case, would help determine the possibility of using genetic approaches to individualize the manipulation of training variables. This would have important implications in sport science where genetic specific training programs would enhance competitive abilities. In addition, it would help talent identification for appropriate athletic events. These numerous implications supply motivation for further genetic studies of muscle hypertrophy and muscle strength. The importance of such findings would not end at sports science.

An improved understanding of the exact mechanisms involved in the development of muscle strength and hypertrophy may eventually lead to the development of pharmaceuticals for use in a clinical setting. This comes with great importance especially for clinical populations that are at risk of muscle atrophy or sarcopenia. Therefore, the implications of future discoveries would be extremely important being useful in various fields such as sports science, aging and rehabilitation.

*The authors declare that there are no conflicts of interest.

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