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## Mechanisms of Cachexia in Chronic Disease States

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### Abstract

Sarcopenia and cachexia are muscle wasting syndromes associated with aging and with many chronic diseases such as congestive heart failure (CHF), diabetes, cancer, chronic obstructive pulmonary disease and chronic kidney disease (CKD). While mechanisms are complex these conditions are often accompanied by elevated angiotensin II (Ang II). Patients with advanced CHF or CKD often have increased Ang II levels and cachexia, and angiotensin-converting enzyme (ACE) inhibitor treatment improves weight loss. We found that Ang II infusion in rodents leads to skeletal muscle wasting. Ang II increases cytokines and circulating hormones such as tumor necrosis factor- $\alpha$ , interleukin-6, serum amyloid-A and glucocorticoids, which regulate muscle protein synthesis and degradation. Ang II-induced muscle wasting is caused by alterations in insulin-like growth factor-1 signaling, enhanced muscle protein breakdown via the ubiquitin-proteasome system, and decreased appetite resulting from downregulation of hypothalamic orexigenic neuropeptides such as Npy and orexin. Ang II also inhibits 5' AMP-activated protein kinase (AMPK) activity and disrupts normal energy balance via activation of AMPK phosphatase PP2C $\alpha$ . Furthermore, Ang II inhibits skeletal muscle stem (satellite) cell proliferation, leading to lowered muscle regenerative capacity. Distinct satellite cell angiotensin receptor subtypes have different effects on different stages of differentiation and are critical for regulation of muscle regeneration. These data suggest that the renin-angiotensin system (RAS) plays a critical role in mechanisms underlying cachexia in chronic disease states, and is a promising target for the treatment of muscle atrophy in patients with diseases such as CHF and CKD.

### Introduction

Patients with cachexia, or wasting syndrome, develop weight loss, muscle atrophy, fatigue, weakness, and often loss of appetite without actively trying to lose weight. Cachexia patients are defined as those that lose more than 5% of body weight over 12 months or less in the presence of a chronic disease such as congestive heart failure (CHF), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) and cancer. 10–30% of the patients with these diseases develop cachexia, and it affects more than 5 million people in the United States<sup>1</sup>. Cachexia is a multifactorial disease and, importantly, nutritional support cannot fully reverse the syndrome. In cachexia conditions, the degradation of myofibrillar proteins is increased and protein synthesis is decreased, leading to the rapid loss of muscle mass.

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Weight loss and reduced muscle mass are associated with a reduction in quality of life and increased mortality. Thus cachexia is a major public health issue, and the development of interventions to block or attenuate this process would have significant therapeutic benefits in a wide array of chronic diseases.

## Mechanisms and potential therapies for cachexia

Among the candidate mediators of cachexia that have been investigated, proinflammatory cytokine tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is the most prominent and well characterized factor. TNF- $\alpha$  has been shown to induce cachexia in mice,<sup>2</sup> and to cause myotube atrophy *in vitro* via activation of E3 ubiquitin ligases.<sup>3</sup> Although many rodent tumor models of cancer cachexia showed increased TNF- $\alpha$ ,<sup>4</sup> the relevance of TNF- $\alpha$  to human cancer cachexia is unclear. Maltoni et al found that circulating levels of TNF- $\alpha$  in cancer cachexia patients had no correlation with weight loss and anorexia.<sup>5</sup> Furthermore, a clinical trial designed to block TNF- $\alpha$  signaling using anti-TNF- $\alpha$  antibody (infliximab) in cancer cachexia patients closed early because the treatment prevented or palliated cancer-associated weight loss, and patients developed greater fatigue and worse global quality of life scores.<sup>6</sup>

Another candidate mediator of cachexia is interleukin-6 (IL-6). It has been shown that different kinds of cancer cells secrete IL-6 and that circulating levels of IL-6 correlate with weight loss in cancer patients in some,<sup>7,8</sup> but not all,<sup>5</sup> studies. Strassmann et al showed that increasing levels of IL-6 in tumor bearing mice correlated with the development of cachexia, and that an antibody against IL-6, but not against TNF- $\alpha$ , suppressed cachexia development.<sup>9</sup> However, a clinical trial of IL-6 antibody in weight-losing lung cancer patients did not have significant effect on loss of lean body mass, although anorexia, fatigue and anemia were prevented.<sup>10</sup>

Myostatin and Activin A are the most recent and promising target molecules related to cancer cachexia. Myostatin and Activin A are members of the transforming growth factor- $\beta$  (TGF- $\beta$ ) family, and are both upregulated in patients with various kinds of wasting diseases.<sup>11</sup> Animals and humans with null mutations of myostatin show dramatic muscle hypertrophy<sup>12,13</sup> and blockade of Activin-A restored regenerative capacity of human myoblasts in the presence of high cytokines (TNF- $\alpha$  or IL-1 $\beta$ )<sup>14</sup>. Myostatin and Activin-A signal through the common receptor, Activin type II receptor B (ActRIIB). To inhibit both myostatin and Activin A signaling at the same time, soluble ActRIIB-Fc decoy protein (sActRIIB) was developed. Treatment of tumor-bearing mice with sActRIIB prevented cachexia development without affecting the tumor growth, and prolonged survival.<sup>15</sup> Thus blockade of ActRIIB signaling seems to be a very promising treatment of cancer cachexia and clinical trials are ongoing to treat patients with sarcopenia and cachexia.<sup>16</sup>

Cachectic patients with CHF showed increased growth hormone (GH) levels with lower insulin-like growth factor-1 (IGF-1), suggesting GH resistance.<sup>17</sup> Also, it has been shown that CHF patients had higher glucose and insulin levels, an indication of insulin resistance.<sup>18</sup> Since CHF patients have higher Ang II levels and Ang II causes insulin resistance in skeletal muscle by inhibiting insulin-stimulated GLUT4 translocation,<sup>19,20</sup> it was postulated that blockade of Ang II could benefit skeletal muscle function in chronic diseases with high

levels of Ang II. There are 2 main pharmacological approaches to target the effects of Ang II: inhibiting the formation of Ang II by angiotensin converting enzyme inhibitor (ACEi) and blocking the AT1R by angiotensin receptor blocker (ARB). Because alternative ACE-independent pathways of Ang II formation exist, the use of ARB could be more specific in targeting Ang II-mediated muscle wasting. The ACEi enalapril was shown to reduce the risk of weight loss in CHF patients<sup>21</sup> and ACEi helped maintain body weight but not muscle strength in patients with CHF or hypertension.<sup>22</sup> Elderly patients without heart failure on antihypertensive treatment with ACEi had higher muscle mass than patients receiving other anti-hypertensive therapy.<sup>23</sup> In addition, insulin sensitivity was improved by losartan and lisinopril in hypertensive patients.<sup>24</sup> There have been a few clinical trials designed to protect muscle wasting by blocking Ang II. Ark Therapeutics has completed a phase III clinical trial treating cancer cachexia patients with the ACE inhibitor imidapril. Imidapril prevented weight loss in non-small cell lung cancer and colorectal cancer, but not in pancreatic cancer, but its effect to prevent weight loss did not reach statistical significance when the data were combined. The company discontinued development of the product after the failed clinical trial, although it remains convinced of the value of this approach.<sup>25,26</sup> Blockade of AT1R signaling could be another approach to prevent weight loss in cachexia patients, but Merck & Co. Inc., which marketed losartan as Cozaar, has no plans to develop it for new indications in the U.S., since it went off patent.<sup>26</sup>

One of the potential reasons why clinical trials of Ang II blockade have so far been unsuccessful is that the underlying mechanisms of renin-angiotensin system-mediated muscle wasting is not fully understood. For instance, Ang II and other angiotensins act on different subtypes of receptors such as AT1R, AT2R, Mas and IRAP.<sup>27</sup> Because ACEi blocks conversion of Ang I to Ang II, ACEi treatment results in a decrease of Ang II, whereas Ang I level is increased. On the other hand, blockade of AT1R by ARB results in a compensatory increase of Ang II, which may activate AT2R-mediated signaling. Thus, it is critical to understand the multiple signaling pathways that mediate the effect of the RAS. Current progress in understanding the role of the RAS in muscle wasting is summarized and discussed below.

## Ang II and muscle wasting

It was first demonstrated that Ang II infusion in the rat caused a significant loss of body weight through 2 independent mechanisms, a reduction of food intake and increased proteolysis in skeletal muscle.<sup>28</sup> Both of these effects were completely prevented by losartan, but not by the vasodilator hydralazine, showing that Ang II causes wasting through the AT1R and that its effect is independent of blood pressure regulation. It was found that Ang II caused an increase of muscle protein breakdown via the ubiquitin-proteasome system (UPS). Accelerated proteolysis via the UPS plays a major role in muscle atrophy in several different types of cachexia.<sup>29</sup> The muscle specific E3 ubiquitin ligases atrogen-1 and muscle RING finger-1 (MuRF-1) were identified as genes strongly upregulated in different muscle atrophy conditions, and knockout mice for either of these genes partially prevented muscle wasting.<sup>30</sup> In Ang II-induced muscle wasting, expression of atrogen-1 and MuRF-1, levels of ubiquitin-conjugated proteins and 20S proteasome activity were robustly increased.<sup>31-33</sup>

In the Ang II-induced wasting condition, it was also found a decrease of skeletal muscle IGF-1 signaling which is the main anabolic pathway in skeletal muscle.<sup>28,34</sup> IGF-1 modulates muscle size via autocrine and paracrine signals, by directly stimulating protein anabolism in myofibers and by activation of satellite cell proliferation.<sup>35</sup> IGF-1 signals through PI3K/Akt and induces muscle hypertrophy by stimulating GSK and mTOR kinases, which regulate protein translation.<sup>36</sup> Multiple studies have shown the involvement of IGF-1/PI3K/Akt signaling in muscle cell size regulation and atrophy. For instance, inhibition of PI3K and expression of dominant-negative Akt reduce the size of myotubes *in vitro*,<sup>37</sup> in mice deficient for Akt1 and Akt2 have smaller muscle size<sup>38</sup> and activation of Akt in rat muscle prevents denervation-induced atrophy.<sup>36,39</sup> The authors utilized a transgenic mouse strain in which IGF-1 is overexpressed under the control of a skeletal muscle specific promoter<sup>40</sup> and showed that the local increase of IGF-1 could prevent Ang II-induced muscle wasting.<sup>31</sup> Interestingly, although Ang II rapidly increased both atrogen-1 and MuRF-1 expression, IGF-1 prevented only the increase in atrogen-1.<sup>32</sup> These data may be consistent with the current evidence suggesting the distinct roles of atrogen-1 and MuRF-1 in muscle wasting.<sup>41</sup> Myofibrillar proteins have been identified as the target of MuRF-1<sup>42,43</sup> and it is suggested that MuRF-1 is likely involved in skeletal muscle proteolysis. On the other hand, atrogen-1 has been shown to target MyoD, the regulator of myogenesis, and eIF- $\epsilon$ , the eukaryotic initiation factor of protein synthesis, suggesting that its main role is the regulation of protein synthesis.<sup>44,45</sup> Although precise signaling pathways whereby Ang II and IGF-1 regulate Atrogen-1 and MuRF-1 remain to be elucidated, it is of note that atrogen-1 and MuRF-1 are regulated by distinct mechanisms.<sup>46,47</sup> In summary, Ang II and IGF-1 have opposing roles in regulating muscle protein synthesis and degradation. Disruption of IGF-1 signaling by Ang II plays a critical role in Ang II-induced atrophy, and local activation of IGF-1 signaling can prevent Ang II-induced muscle wasting.

There have been studies reporting that the effect of Ang II to cause muscle wasting is via the direct action of Ang II on skeletal muscle cells and is indirectly mediated by other circulating factors. It has been shown that Ang II directly acts on cultured muscle cells and induces proteolysis via the UPS pathway.<sup>48,49</sup> On the other hand, it has been demonstrated that multiple circulating hormones and cytokines mediate Ang II's action on skeletal muscle. Glucocorticoids are required for activation of the UPS in acidosis and diabetes, and glucocorticoid inhibition restored Ang II-induced loss of muscle mass.<sup>31</sup> After Ang II infusion, there is an increase of circulating IL-6 and serum amyloid-A (SAA), and blockade of IL-6/SAA prevented Ang II-induced wasting.<sup>50</sup> These studies suggest that the catabolic effect of Ang II on skeletal muscle *in vivo* is, at least in part, mediated via intermediate molecules activated by Ang II.

## Ang II and oxidative stress

Reactive oxygen species (ROS) play an important role in Ang II-induced signaling in different cell types, contributing to cardiac myocyte and vascular smooth muscle cell hypertrophy, endothelial dysfunction, hypertension, and insulin resistance.<sup>51,52</sup> Ang II has been shown to induce ROS generation in skeletal muscle,<sup>53,54</sup> and ROS contributes to disuse muscle atrophy.<sup>55</sup> NADPH oxidase and mitochondria are major sources of ROS in atrophied skeletal muscles.<sup>56,57</sup> Oxidative stress induces proteolysis and atrophy via several

different mechanisms: (1) calcium overload and activation of calcium-activated proteases such as calpain; (2) stimulation of the 20S proteasome system via activation of caspase-3; (3) activation of E3 ubiquitin ligases atrogin-1 and MuRF-1. Ang II-induced proteolysis is prevented by antioxidants in myotubes<sup>49</sup>, and genetic or pharmacological inhibition of NADPH oxidase blocked Ang II-induced 20S proteasome activity and muscle wasting.<sup>33</sup> Ang II also increases mitochondrial ROS formation<sup>58,59</sup> and it has been speculated that NADPH oxidase-induced ROS could directly stimulate the mitochondria.<sup>59</sup> However, the mitochondrial-targeted antioxidant Mito-TEMPO failed to prevent Ang II-induced muscle wasting, suggesting that mitochondrial ROS are not directly involved.<sup>60</sup> These data suggest that specific targeting of ROS and NADPH oxidase could be a beneficial, novel therapy to treat Ang II-induced wasting.

## Ang II and energy balance

It has been proposed that a common set of molecular mechanisms underlie muscle wasting in different chronic diseases. DNA microarray analysis in different atrophying conditions revealed that the group of genes required for ATP production and late steps in glycolysis is commonly downregulated.<sup>61</sup> These changes would suppress muscle's capacity to utilize glucose and reduce muscle energy production. Reduced glucose utilization has been observed in the setting of cancer and renal failure, and thus disruption of metabolic homeostasis could be one of the mechanisms involved in development of cachexia.

Yoshida and Delafontaine analyzed metabolic changes in the Ang II-induced wasting condition and found that Ang II depletes skeletal muscle ATP content and causes muscle wasting likely via induction of mitochondrial dysfunction.<sup>60</sup> This reduction of ATP is caused by decreased activity of AMPK, a cellular sensor of energy status. When the cellular energy status is low (high AMP:ATP ratio) AMPK activates ATP synthesis, and data indicate that Ang II causes muscle wasting in part by preventing skeletal muscle homeostatic capacity to maintain energy balance. The AMPK activator 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) reversed Ang II-induced inhibition of AMPK, leading to restoration of ATP levels and inhibition of the Ang II-induced muscle wasting. AICAR also blocked Ang II-induced E3 ubiquitin ligases atrogin-1 and MuRF-1 expression. Contrary to these authors' findings, in S6 kinase-1 deficient mice there was increased AMP levels, AMPK upregulation and muscle atrophy.<sup>62</sup> In these mice, AMPK inhibition restores muscle cell growth and sensitivity to nutrient signals. Also, it has been reported that AMPK-mediated phosphorylation of FoxO activates E3 ubiquitin ligase expression in muscle cell culture *in vitro*.<sup>63</sup> However, in Ang II infused animals the net effect of AMPK activation by AICAR is Akt activation and inhibitory phosphorylation of FoxO1, which could explain the ability of AICAR to abrogate Ang II-mediated E3 ubiquitin ligase induction. Importantly, the authors found that the Ang II-induced reduction of AMPK activity is mediated by upregulation of the upstream phosphatase PP2C $\alpha$ , and PP2C $\alpha$  knockdown restored mitochondrial function and muscle wasting in Ang II infused animals.<sup>64</sup> Although the precise mechanism whereby Ang II inhibits AMPK via upregulation of PP2C $\alpha$  remains to be elucidated, these data suggest a therapeutic potential of targeting PP2C $\alpha$  in chronic wasting conditions with increased Ang II levels.

## Ang II reduces appetite

In 2008, Evans et al<sup>65</sup> proposed the diagnosis of cachexia to be based on at least 5% weight loss in 12 months or less in the presence of underlying illness, plus 3 of the 5 following criteria: 1) Decreased muscle strength, 2) Fatigue, 3) Anorexia, 4) Low-fat free mass index and 5) Abnormal biochemistry (increased inflammatory markers (CRP, IL-6), anemia and low serum albumin). As can be seen in this definition, anorexia is frequently, if not always, associated with wasting, and anorexia and loss of body fat is a powerful predictor of mortality in cancer cachexia patients.<sup>66</sup> Food intake is regulated by complex mechanisms that involve the actions of hypothalamic orexigenic/anorexigenic neuropeptides and circulating factors secreted from peripheral organs (e.g. adipose tissues and gastrointestinal tract). These authors found that Ang II causes wasting through 2 different mechanisms: increased protein catabolism in skeletal muscle and loss of food intake.<sup>28</sup> Pair-feeding experiments were performed, in which a group of animals received an identical amount of food as Ang II-infused animals, and found that approximately 80% loss of body weight in Ang II-infused animals is due to reduced food intake. Consistent with these data, AT1R deficient mice are hyperphagic and obese. Furthermore, multiple studies have shown that intracerebroventricular (icv) infusion of Ang II caused reduced food intake and changes in orexigenic/anorexigenic neuropeptides such as agouti-related protein (AgRP), proopiomelanocortin (POMC), thyrotropin-releasing hormone (TRH), CRH, neuropeptide-Y (Npy) and orexin,<sup>67-70</sup> suggesting that systemically increased Ang II in chronic diseases could directly act on hypothalamic neurons to regulate food intake by modulating orexigenic/anorexigenic neuropeptide expressions. Indeed, it has been shown that the AT1R is expressed in multiple hypothalamic neurons, including the lateral hypothalamic area, paraventricular nucleus, retrochiasmatic area and perifornical nucleus.<sup>71</sup>

## RAS and muscle regeneration

Skeletal muscle has a remarkable ability to maintain its homeostasis against injury or wasting by activating a well orchestrated regenerative response to repair damaged myofibers. Injury leads to activation and proliferation of mitotically quiescent mononuclear cells, satellite cells, which form myoblasts, terminally differentiate and fuse to form multinucleated myotubes<sup>72</sup>. Muscle atrophy occurs in a variety of pathophysiological conditions, including disuse, denervation, starvation, sarcopenia and cachexia, but the response of satellite cells in these conditions is not well characterized. In cancer cachexia animal models, it has been suggested that there is less regeneration and possibly a reduction of satellite cell function.<sup>73-75</sup> The most well characterized atrophy-associated regeneration condition is sarcopenia. It has been shown that aged satellite cells display reduced proliferative response and regenerative capacity<sup>76,77</sup>. Satellite cell proliferation is regulated by Notch signaling and lowered Notch activity is responsible for the reduced proliferative capacity of aged satellite cells.<sup>76,78</sup> In the aged skeletal muscle, there is an increase of TGF- $\beta$  expression and activated p-Smad3 counteracts Notch and inhibits cell cycle progression, thus causing lower satellite cell proliferative capacity.<sup>79</sup> Also, fibroblast growth factor-2 (FGF2) expression is increased in aged skeletal muscle and increased FGF2 disrupts satellite cell quiescence and self-renewing activity,<sup>77</sup> which leads to lower satellite cell regenerative capacity. Importantly, impaired regeneration in aged mice is reversible by exposure to a



young circulation,<sup>80</sup> and growth differentiation factor-11 (GDF11) has recently been identified as a factor that maintains satellite cells in a “young” state.<sup>81</sup> Although it is not clear whether the same mechanisms could lead to lower satellite cell function in chronic disease states, studies in aged muscle clearly indicate that systemic changes strongly affect satellite cell regenerative capacity. Therefore, identifying mechanisms whereby chronic diseases lead to lower satellite cell function would have the therapeutic potential to reverse the reduction in muscle regeneration seen in cachexia conditions.

Multiple studies have suggested a role of Ang II in regulating satellite cell function, and considering the potential involvement of Ang II in muscle wasting in many chronic diseases,<sup>48,82–85</sup> Ang II could be a systemic factor that affects satellite cell function in disease states. However, the consequence of an increase in Ang II on satellite cell function is controversial. Cohn et al<sup>86</sup> first reported that the effect of AT1R blockade by losartan improved muscle regeneration in mouse models of myopathy through suppression of TGF- $\beta$ . Consistent with this study, it is reported that losartan improved muscle regeneration and decreased fibrosis after laceration-induced injury.<sup>87</sup> Burks et al showed that losartan treatment blocked TGF- $\beta$  signaling and losartan-treated mice developed significantly less fibrosis and exhibited improved muscle function after cardiotoxin-induced injury. In addition, immobilized mice treated with losartan were protected against loss of muscle mass. Interestingly, however, this muscle wasting-protective effect of losartan was not mediated by TGF- $\beta$ , but by increased IGF-1/Akt/mTOR signaling, suggesting AT1R signaling modulates different signaling cascades in regeneration and atrophy.<sup>88</sup> On the other hand, ACE inhibition or genetic ablation of AT1R have been reported to impair skeletal muscle regeneration.<sup>89</sup> Murphy et al also reported that muscle regenerative capacity was impaired in AT1R knockout mice, although they found muscle strength and locomotor activity were paradoxically enhanced.<sup>90</sup> Since none of these studies directly analyzed the effect of Ang II on satellite cells *in vivo*, animals were infused with Ang II in the setting of muscle injury-induced regeneration.<sup>91</sup> It was found that Ang II infusion suppressed Notch signaling in satellite cells, leading to impaired satellite cell proliferation and reduced regeneration. Importantly, quiescent and proliferating satellite cells highly express AT1R, whereas it declines after cells are differentiated into myotubes. These data are consistent with a suppressive role for Ang II on satellite cell function and muscle regeneration. The conflicting data reported for the function of Ang II on satellite cells could be because of the different experimental settings utilizing pharmacological inhibitors or genetic deletion of the AT1R. Caution should be exercised when analyzing RAS effects resulting from inhibition of 1 part of the entire system. The RAS includes multiple angiotensins and receptors, and it is not fully understood how different angiotensin ligands and receptors act in orchestration. For instance, inhibition of Ang II production by ACEi would result in an increase of its precursor Ang I, whereas blockade of Ang II signaling by AT1R blocker would increase Ang II through a compensatory mechanism. Indeed, the authors recently found that another Ang II receptor AT2R positively regulates satellite cell differentiation and fusion process.<sup>92</sup> Considering the antagonistic action of AT1R and AT2R,<sup>93</sup> these data indicate that AT1R and AT2R counteract each other and regulate different stages of satellite cell differentiation processes. Furthermore, Acuña et al reported that another angiotensin ligand Ang (1–7) restored muscle strength through inhibition of TGF- $\beta$ .<sup>94</sup> Although complete mechanisms

underlying RAS-mediated regulation of satellite cell function are complex and remain to be elucidated, these studies suggest that the RAS, via the actions of multiple angiotensin ligands and their receptors, regulates satellite cell function in physiological conditions, and that alterations in RAS effects in pathophysiological states may lead to impaired satellite cell function.

## Future prospects

There have been a growing number of studies related to cachexia and our understanding of underlying mechanisms of loss of muscle mass in chronic disease conditions has made substantial progress in recent years. Approaches to prevent or attenuate cachexia are urgently needed and several promising therapies are under investigation in clinical trials. A major challenge underlying the development of cachexia treatment is the complex and multifactorial nature of the disease. It is unlikely that 1 therapeutic intervention could be effective in all the cachexia conditions associated with different chronic diseases. The RAS is activated in many chronic diseases such as CHF, CKD, COPD and cancer and in this manuscript the authors have summarized and discussed the involvement of the RAS in the development of muscle wasting. Studies have shown that Ang II induces muscle wasting through multiple mechanisms: (1) Increased protein breakdown via reduced IGF-1 and increased cytokine signaling such as glucocorticoid and IL-6; (2) Increased oxidative stress via activation of NADPH oxidase; (3) Impaired energy balance via inhibition of AMPK; (4) Reduced appetite via alteration of orexigenic/anorexigenic neuropeptide expression in the hypothalamus; (5) Inhibition of satellite cell function and muscle regeneration. It is likely that Ang II causes muscle wasting via a combination of these effects (Fig. 1), and recent evidence suggests that other RAS components play important roles in skeletal muscle physiology. Future studies are required to elucidate the RAS-mediated regulation of skeletal muscle and satellite cell function to connect these findings to the development of effective therapies for cachexia.

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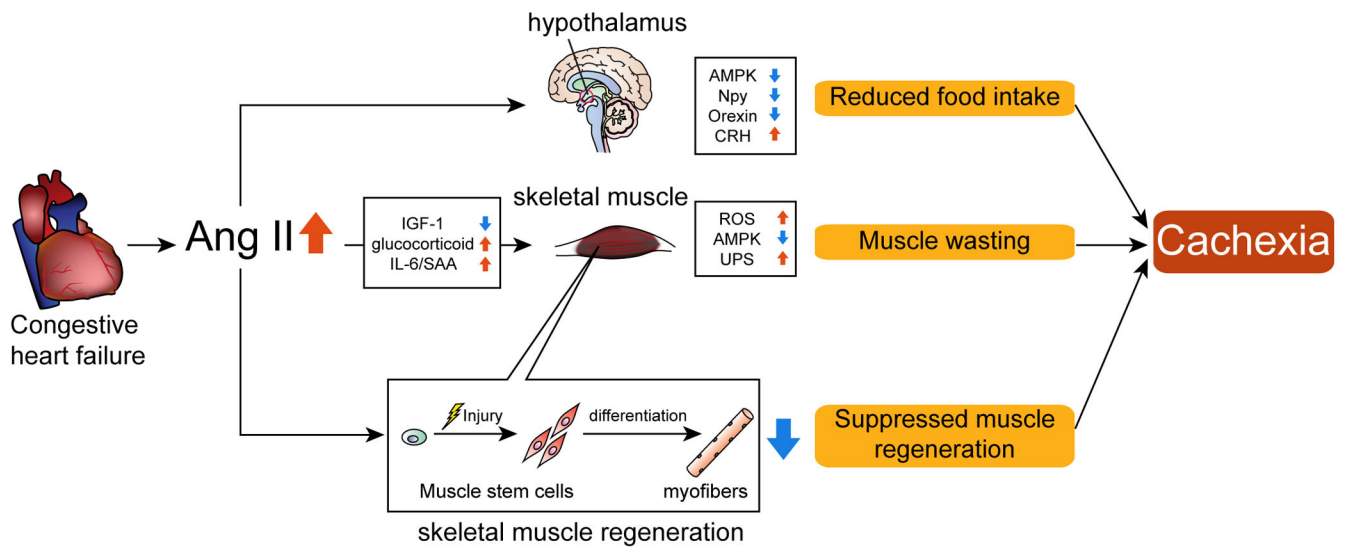
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**Fig. 1.**

Ang II-induced muscle wasting: potential mechanisms of cardiac cachexia.

In CHF patients, there is an increase of Ang II. Increased Ang II causes a reduction of IGF-1 and increased glucocorticoids and IL-6/SAA, which result in muscle wasting. In skeletal muscle, there is an increase of ROS, reduction of AMPK and increased UPS, all of which result in muscle proteolysis. Ang II also acts on hypothalamic neurons to reduce appetite via alterations of orexigenic/anorexigenic neuropeptide expression. Reduced appetite leads to muscle wasting due to insufficient energy intake to maintain muscle mass. Ang II prevents satellite cell proliferation and skeletal muscle regeneration via inhibition of Notch signaling. The combination of Ang II-induced muscle wasting, reduced food intake and lower muscle regeneration lead to the development of cachexia.