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Review

Curcumin and muscle wasting—A new role for an old drug?

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Abstract Sepsis, severe injury, and cancer are associated with loss of muscle mass. Muscle wasting in these conditions is mainly caused by increased proteolysis, at least in part regulated by nuclear factor-κB. Despite recent progress in the understanding of mediators and mechanisms involved in muscle wasting, effective and universally accepted treatments by which muscle atrophy can be prevented or reversed are still lacking. We review recent evidence suggesting that curcumin (diferuloylmethane), a component of the spice turmeric, may prevent loss of muscle mass during sepsis and endotoxemia and may stimulate muscle regeneration after traumatic injury. Curcumin has been part of the traditional Asian medicine for centuries, mainly because of its anti-inflammatory properties. Studies suggest that inhibition of nuclear factor-κB is one of the mechanisms by which curcumin exerts its ant-inflammatory effects. Curcumin is easily accessible, inexpensive, and non-toxic even at high doses, and may therefore offer an important treatment modality in muscle wasting and injury. It should be noted, however, that the muscle-sparing effects of curcumin are not universally accepted, and more studies are therefore needed to further test the role of curcumin in the prevention and treatment of muscle wasting.

Keywords: Muscle atrophy; Proteolysis; Nuclear factor-κB; Catabolic

Introduction

Curcumin (diferuloylmethane), a component of the spice turmeric (*Curcuma longa*) and responsible for the yellow color of curry, has been part of the traditional Asian medicine for centuries [1,2]. The list of ailments for which curcumin has been used is long and includes respiratory conditions, liver disorders, anorexia, rheumatism, common colds, and sinusitis [2,3]. An area in which the use of curcumin has been particularly prevalent is promotion of wound healing [1], but it has also been used as an anti-inflammatory and an anticancer treatment [2,3].

Several recent studies have focused on mechanisms by which curcumin may exert its beneficial effects. In particular, mechanisms accounting for the anti-inflammatory effects of curcumin have been examined. Such mechanisms include inhibition of nuclear factor-κB (NF-κB) activity, at least in part reflecting inhibition of IκB kinase activity [4,5]. Inhibition of NF-κB activity is of particular interest for the potential use of curcumin in the treatment of muscle wasting because NF-κB activation is an important mechanism for loss of muscle mass [6–10]. Other mechanisms by which curcumin may exert anti-inflammatory effects include activation of the heat-shock response [11], inhibition of p38 kinase activity [12,13] and oxygen free radical formation [14], and prevention of cytokine production and release [5].

The growing interest for curcumin in Western medicine is illustrated by several ongoing clinical trials, the majority of which are being conducted in the United States. In a recent review of traditional medicines [2], seven current clinical trials were listed testing the effects of curcumin in the treatment of colon and pancreatic cancers, Alzheimer's disease, chemotherapy-induced mucositis, multiple myeloma, psoriasis, and cystic fibrosis. In addition, a clinical trial investigating the use of curcumin in patients with familial adenomatous polyposis is being conducted [1].

The purpose of this review is to discuss the potential use of curcumin in the prevention and treatment of muscle wasting, in particular sepsis-induced muscle wasting. Aspects on the beneficial effects of curcumin in sepsis, other

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than prevention of loss of muscle mass, were reviewed recently elsewhere [15].

Muscle wasting in sepsis and other catabolic conditions

Under normal conditions, muscle mass is maintained by a balance between protein synthesis and degradation and muscle wasting can occur when this balance is perturbed. Muscle wasting continues to be a significant clinical problem in patients with various catabolic conditions, including sepsis, acquired immunodeficiency syndrome, severe injury, uremia, heart failure, cancer, and starvation [16]. There is evidence that muscle atrophy in these conditions mainly reflects increased breakdown of myofibrillar proteins [17,18], although inhibited protein synthesis may also contribute to the loss of muscle proteins [19]. Increased protein breakdown in atrophying muscle reflects upregulated expression and activity of multiple proteolytic pathways, including lysosomal, calcium-calpain–, and ubiquitin-proteasome–dependent mechanisms [16–18]. Among these mechanisms, activation of the ubiquitin-proteasome system is particularly important and is accompanied by a substantial increase in the expression of the muscle-specific ubiquitin ligases atrogin-1 and Muscle Ring Finger 1 (MuRF1) [20–22].

Loss of muscle mass in catabolic patients results in weakness, fatigue, and delayed ambulation during sickness, with increased risk for thromboembolic and pulmonary complications. Prolonged bedrest in itself accelerates the degradation of muscle proteins, thus creating a vicious cycle [23]. The molecular regulation of muscle protein turnover in atrophying muscle and the clinical consequences of muscle wasting have been reviewed in recent papers [16–19].

A widely accepted treatment of muscle wasting is lacking

Despite substantial progress during the past two decades in our understanding of mediators and mechanisms involved in muscle atrophy, we still do not have an effective, universally accepted treatment by which muscle wasting can be prevented or reversed in critically ill patients. The lack of a generally accepted treatment of muscle wasting is reflected by the large number of different regimens that have been proposed in recent studies, including administration of anabolic hormones [24–26], creatine [27], branched-chain amino acids [28], and factors counteracting myostatin [29,30]. Many of these treatments may be costly, are still experimental, and will have to await clinical testing.

Curcumin is easily available, inexpensive, and has proven non-toxic even when administered at high doses [1,31–35]. One potential problem with curcumin is its relatively low bioavailability, requiring high doses that may be associated with bad taste and odor [33,34]. Ongoing research aimed at overcoming this hurdle includes the development of "nanocurcumin", i.e., administration of curcumin at high doses in nanoparticles that are hydrophilic on the exterior and hydrophobic on the interior [1]. The hydrophilic exterior allows nanocurcumin to be soluble in water, which makes it possible for the particles to enter the blood stream where the biodegradable polymer nanoparticles break down and release the drug. Interestingly, nanocurcumin has been reported to kill cultured pancreatic cancer cells in the laboratory setting [1]. Another method to increase the bioavailability of curcumin is to add piperine (found in black pepper), which increases the uptake of curcumin by 2000% in humans. This approach is used in the development of curcumin-based drugs for the treatment of malaria [1]. Considering the growing interest for curcumin in Western medicine and an increasing list of potential indications for its use, it can be predicted that there will be a rapid development of new and innovative delivery systems for the drug. Because such systems can be patented (as opposed to the use of the drug itself), more resources from pharmaceutical companies may become available in the future for the development of curcumin formulations.

Role of NF-κB activation in muscle wasting

The molecular regulation of muscle wasting is complex and involves activation of various transcription factors and nuclear cofactors that regulate genes in different proteolytic pathways (reviewed by Hasselgren [36,37]). Among transcription factors that are activated in atrophying muscle, NF-κB is particularly important, with several lines of evidence supporting a role of NF-κB in muscle wasting. We reported previously that NF-κB DNA binding activity was increased in skeletal muscle of septic rats [6]. Interestingly, the response to sepsis of NF-κB was biphasic, with an early activation and subsequent inhibition of NF-κB activity, possibly reflecting the influence of different mediators of muscle wasting (such as cytokines and glucocorticoids). In addition to sepsis, other catabolic conditions are associated with NF-κB activation in muscle, including cancer [10], disuse atrophy [38], and muscle denervation [39]. In other studies, treatment of cultured myotubes with tumor necrosis factor-α and interferon-γ resulted in biphasic NF-κB activation [8], and cytokine-induced protein degradation in cultured muscle cells was NF-κB dependent [7]. Recent experiments, using a pharmacologic inhibitor of NF-κB, have suggested that NF-κB is also involved in muscle wasting caused by muscular dystrophy [40].

In recent experiments, genetic evidence was provided for a role of NF-κB in the development of muscle wasting [9]. In those experiments, transgenic mice with muscle-specific overexpression of activated IκB kinase displayed increased NF-κB activity and a substantial loss of muscle mass. When these mice were crossed with transgenic mice with muscle-specific overexpression of an IκBα "super-repressor" (IκBα