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REVIEW

An overview of amines as nutritional supplements to counteract cancer cachexia

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Abstract Cancer cachexia is a complex multifactorial syndrome characterized by loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Recently, some amino acids and other amine dietary supplements have been highlighted in medical field due to positive effects upon diseases evolving skeletal muscle atrophy. Therefore, the aim of this brief review is to discuss the putative application of amines as dietary supplements to counteract skeletal muscle wasting on cancer cachexia. Specifically, we focus in two nutritional supplements: (1) branched-chain amino acids (BCAAs) and (2) creatine. Both BCAAs and creatine may attenuate proteolysis and enhance proteins synthesis in skeletal muscle. Although more experimental studies and clinical trials are still necessary to elucidate this therapeutic application, several evidences have demonstrated that amines supplementation is a promising coadjuvant treatment to cancer cachexia.

Keywords Muscle atrophy · Wasting disease · Amino acids · BCAA · Creatine

1 Introduction

Cachexia is associated with approximately 80 % of severe cancer cases [1, 2] and it is responsible for more than 30 % of the deaths [3]. Cancer cachexia is a complex multifactorial syndrome characterized by loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment [4]. In fact, loss of skeletal muscle results in impaired daily activities, ultimately leading to respiratory failure and death. In this context, the lack of success of unimodal treatment led to the view that cachexia intervention should include multimodal treatment. Therefore, in order to mitigate severe changes on skeletal muscle metabolism and tropism, non-pharmacological strategies such as exercise training and nutritional supplementation have been considered as a coadjuvant treatment [3, 5, 6].

Amines are moderately polar organic substances containing a nitrogen atom with a lone pair. A large number of medically and biologically important compounds content an amine group, such as the 2-phenylethylamines (e.g., adrenaline and noradrenaline), some types of vitamins (e.g., B1 and B6) and neurotransmitters (e.g., acetycholine), and all the existing amino acids. Recently, some amino acids and other dietary supplements including amine groups (e.g., creatine) have been applied in several sports modalities due to their anabolic effects on skeletal muscle [7, 8]. Additionally, these supplements exert positive effects upon several diseases evolving skeletal muscle atrophy [9–11], including cancer [12–16].

Therefore, the aim of this brief review is to discuss the putative application of amines as dietary supplements to counteract skeletal muscle wasting on cancer cachexia. Specifically, we focus in two nutritional supplements: (1) branched-chain amino acids (BCAAs) and (2) creatine. The chemical structures of these supplements are demonstrated in Fig. 1.

2 BCAAs

As showed in the Fig. 1, the BCAAs include three amino acids (i.e., valine, isoleucine, and leucine) with a similar lateral radical chain. They are transaminated in skeletal muscle and

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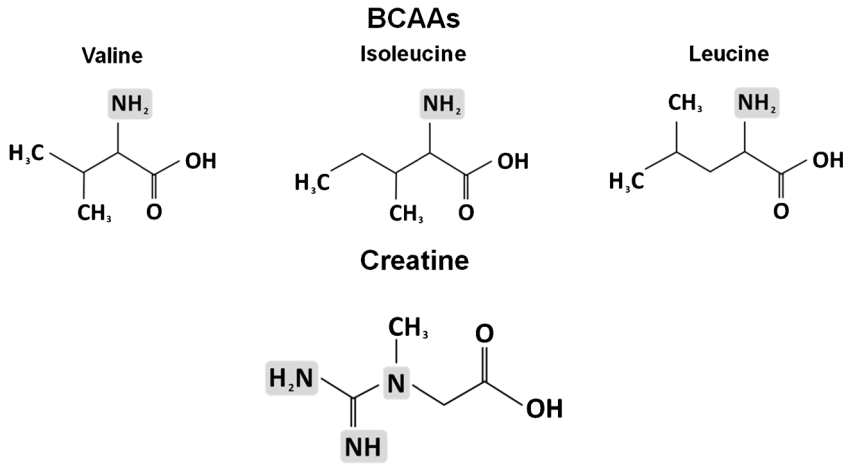

Fig. 1 Chemical structures of branched chain amino acids (BCAAs) and creatine

exert an important role as energy source, along with anti-inflammatory and protein synthesis stimulatory effects [10, 17, 18]. Although the dietary ingestion of BCAAs seems adequate for physically active people, the BCAAs supplementation is suggested to achieve an ergogenic dose effect [19]. In this context, studies in sports science have demonstrated an important role as donors of glucose under glycogen depletion condition during exercise. Briefly, BCAAs, especially leucine, is transaminated in skeletal muscle during exercise, generating acetyl-CoA to the Krebs Cycle. Thus, this amino group can be transaminated to alanine, which can yield glucose in liver through the glucose-alanine cycle, resulting in liver glycogen spare [20]. Moreover, it is hypothesized that BCAAs supplementation may exert a therapeutic effect in disease underlying skeletal muscle wasting. BCAAs may attenuate proteolysis and enhance proteins synthesis in skeletal muscle, mainly through activation of mammalian target of rapamycin (mTOR) pathway and modulation of inflammatory status through glutamine production in situations characterized by lack of glutamine, such as cancer [17, 21]. Considering that skeletal muscle protein synthesis is decreased and the proteolysis is extremely enhanced in cancer cachexia (mainly via inflammatory pathways), it is possible to speculate that BCAAs supplementation might counteract the negative protein turnover in this case.

In fact, for more than two decades ago, some authors [22, 23] showed that BCAAs enriched diet improved amino acid utilization for protein synthesis on skeletal muscle without stimulation of tumor development. Additionally, it is well characterized that anorexia contributes to cachexia syndrome [3, 6]. Thus, the effects of BCCAs as donors of glucose, especially leucine [19], may mitigate the anorexia condition [24, 25] and, therefore, restore the normal protein turnover. In this context, several recent studies have showed positive effects of leucine supplementation per se upon skeletal muscle. Peters et al. (2011) demonstrated that muscle mass wasting was attenuated (in a dose-dependent manner) after leucine supplementation in mice inoculated subcutaneously with tumor cells [26]. In another study, leucine supplementation in rats inoculated with Walker 256 carcinoma demonstrated a slight reduction of muscle mass versus a severe reduction in non-supplemented animals [27]. Moreover, the association of leucine supplementation with aerobic exercise training in Walker tumor-bearing rats has increased protein synthesis in gastrocnemius, leading to higher total net protein content [28]. Ventrucci et al. (2004) found a reduction in proteasome signaling pathways in muscles of pregnant tumor-bearing rats [29]. The same authors also have found that leucine supplementation prevented serum insulin decrease, increased the expression of translation inhibition factors, and caused less protein breakdown, suggesting that leucine supplementation may stimulate protein synthesis and inhibit proteolysis in pregnant tumor-bearing rats [30].

In humans, patients receiving 12 g BCAAs/day during 4 weeks before tumor-removing surgery featured reduced brain free tryptophan and improved food intake [25]. As a limitation, this study presented a small sample size and no blinded design. Moreover, Tayek et al. (1986) observed in a crossover study including ten cancer patients that a formula containing 50 % BCAA (17 % leucine) was able to increase whole body protein synthesis and leucine balance, although no differences were found in the 24-h urinary nitrogen balance between groups [31]. Treatments with different concentrations of BCAAs supplementation were studied in gastric cancer patients. An improvement of metabolism without side effects was observed [32]. Altogether, these observations lead to the hypothesis that BCAAs can ameliorate nitrogen retention on skeletal muscle in cancer patients. However, it is important to note that the most of studies have a small number of patients and/or a poor study designs. Therefore, new randomized blinded placebo-controlled clinical trials are still necessary to confirm the beneficial effects of BCAAs (or leucine *per se*) in cancer patients.

Finally, it is known that ~5 % of leucine is converted into β-hydroxy-β-methylbutyrate (HMβ). HMβ supplementation has also been suggested as a potential nutritional strategy to

counteract muscle wasting by stimulating protein synthesis and decreasing protein breakdown [16]. In fact, HMβ supplementation caused a significant reduction in tumor growth as well as a partial restoration of weight loss and skeletal muscle mass in tumor-bearing rats. It has been suggested that HMB prevents muscle protein degradation through attenuation of proteolysis-inducing factor (PIF) [33, 34]. Unfortunately, the lack of randomized blinded placebo-controlled clinical trials limits any extrapolation to patients [35].

3 Creatine

Creatine (N-aminoiminomethyl-N-methylglycine) exerts an essential role in rapid energy provision during skeletal muscle contraction. Briefly, a reversible reaction catalyzed by creatine kinase transfers an N-phosphoryl group from phosphorylcreatine to adenosine diphosphate, regenerating adenosine triphosphate [36] as illustrated in the Fig. 2.

Creatine is endogenously synthesized or ingested from diet. In addition, creatine can be ingested as a supplement, mainly in your monohydrate form. In fact, creatine supplementation is able to increase intramuscular creatine and phosphorylcreatine content, increasing the energy provision and the skeletal muscle mass and function [37, 38]. Thus, this supplement has been used by athletes [39], and recently, it has been emerged as a treatment to several diseases, including those characterized by skeletal muscle loss and dysfunction (for review, see [9]). For example, creatine supplementation is able to increase skeletal muscle strength in fibromyalgia patients [40] and to mitigate the decline of skeletal muscle function during aging [41].

Regarding to cancer disease, some experimental studies have been conducted to clarify the effects of creatine supplementation. These studies revealed that rodents receiving creatine in their regular diets presented a tumor regression after cancer inoculation [14, 42, 43]. Miller et al. (1993) showed that different doses of creatine supplementation attenuated tumor cell growth in mice after the inoculation of the tumor AC33TC. Although not analyzed in this study, the authors speculated that the tumor cells presented impairment in energy metabolism, resulting in low concentration of creatine as well as an exacerbated activity of the glycolytic pathway. Therefore, creatine supplementation could normalize cellular functions, acting as a therapeutic alternative for cancer control [43]. In the same year, Lillie et al., (1993) showed an increase in creatine kinase B expression in tumor cells and observed an N-phosphorylcyclocreatine accumulation. Consequently, this N-phosphorylcyclocreatine accumulation in tumor cells resulted in a detrimental effect on the tumor growth [44]. Additionally, after the creatine supplementation, Kristensen et al. (1999) also demonstrated a reduction in tumor growth of nude mice carrying a human colon adenocarcinoma LS174T [42].

Recently, Patra et al. 2008 and 2012 reported important findings to this research field. First, this group showed a progressive decrease of phosphocreatine, creatine, and creatine kinase levels on transformation of skeletal muscle into sarcoma. Second, they showed that the anticancer effect of methylglyoxal is significantly augmented in presence of creatine. In addition, the effects of methylglyoxal plus ascorbic acid were further augmented with the creatine supplementation and there were no sign of tumor. Interestingly, creatine and creatine kinase were also significantly elevated with the concomitant regression of tumor [14, 45].

In humans, Norman et al. (2006) conducted a preliminary clinical trial to evaluate the effects of 8 weeks of creatine supplementation as coadjuvant treatment in patients with colorectal cancer. The authors assessed the quality of life, muscle

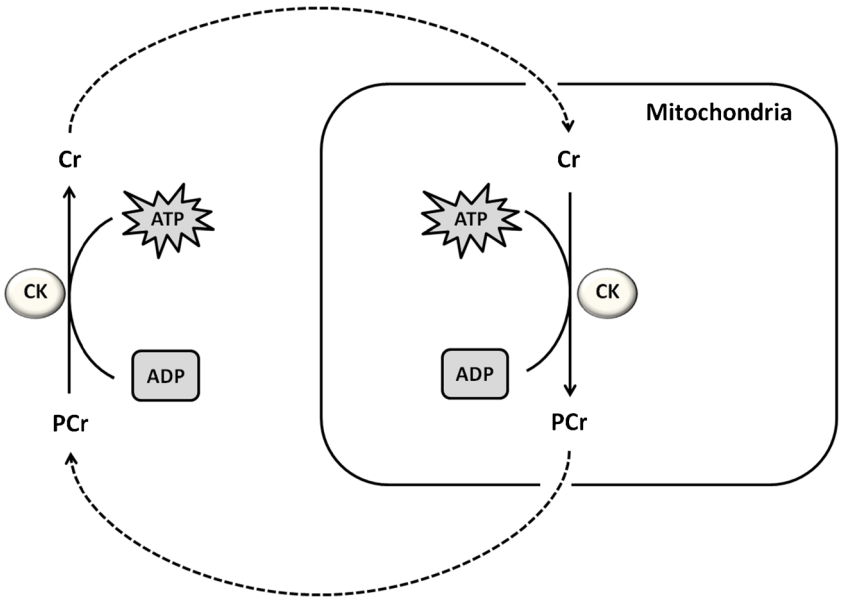

Fig. 2 Illustration of creatine role in rapid energy provision during skeletal muscle contraction. A reversible reaction catalyzed by creatine kinase transfers an N-phosphoryl group from phosphorylcreatine to adenosine diphosphate, regenerating adenosine triphosphate. Afterwards, phosphorylcreatine can be ressinthetized in mitochondria and transported to exert its role in adenosine triphosphate generation in citosol. Creatine kinase (*CK*), adenosine triphosphate (*ATP*), phosphocreatine (*PCr*), adenosine diphosphate (*ADP*)

function, and nutritional parameters of individuals. This study did not found changes in most of the variables analyzed, however, indicated positive effect in handgrip strength test and anthropometric parameters such as capacitance and phase angle. Interestingly, these parameters were correlated with better prognosis in the patients, although these subjects were not considered cachectic during the study [46]. Conversely, it is known that creatine supplementation may counteract the side effects of glucocorticoid administration on skeletal muscle [9]. In order to assess these potential effects, Bourgeois et al. (2008) supplemented with creatine monohydrate nine children with acute lymphoblastic leukemia during two periods of 16 weeks interspaced by a wash out period of 6 weeks. During the supplementation protocol, the children also had been submitted to corticosteroids treatment. The authors found that creatine supplementation had no significant effects on the weight, body mass index, whole body bone mineral content, and fat-free mass. On the other hand, it was observed a reduced gain in body fat on supplemented patients when compared to the control group [13]. This is a pioneer study with humans; however, important limitations need to be addressed. First, the sample was highly heterogeneous (for example: age ranged from 3.5 to 17 years old). Second, different disease stages and corticosteroids treatment were used. Third, this is not a randomized and placebo-controlled trial. Finally, the children did not show weight or skeletal muscle losses. In other words, probably this is not a sample composed by cachectic patients.

Considering that creatine supplementation is able to increase strength, power, and muscle mass in healthy subjects as well as in some types of patients, we encourage the development of randomized trials to investigate the application of creatine supplementation on subjects with a well-characterized cancer cachexia state. In parallel, experiments in vitro or with animals seem absolutely necessary to understand the mechanisms underlying the effects of creatine supplementation to decrease the tumor aggressiveness as well as to mitigate the skeletal muscle atrophy. Altogether, these further studies will help us to clarify the therapeutic effects of creatine supplementation upon cancer cachexia.

Table 1 summarizes the main animal and human studies mentioned in this review.

4 Adverse events

There were no side effects (for any supplement) reported throughout the animal or human studies included in the current review. Actually, no evidences regarding adverse events for BCAAs and creatine supplementation (in adequate doses) have been found in a large spectrum of chronic degenerative diseases. Considering that little is known regarding effects of creatine and BCAAs in tumor cells stimulation, studies showing the safety of nutritional supplements as a primary outcome on cancer cachexia patients are still necessary.

Table 1 Summary of main animal and human studies mentioned in this brief review

Authors	Animals or subjects	Supplementation	Major phenotype effect	Adverse effects
Animal studies				
Miller et al. [43]	Rat mammary, rat sarcoma, and human neuroblastoma tumors-bearing mice	Creatine and cyclocreatine	↓ tumor growth	None
Lillie et al., [44]	ME-180 tumor-bearing mice	Cyclocreatine	↓ tumor growth	None
Kristensen et al., [42]	Colon adenocarcinoma LS174T tumor-bearing mice	Creatine and cyclocreatine	↓ tumor growth	None
Gomes-Marcondes et al., [27]	Walker-256 tumor-bearing rats	Leucine	↓ weight loss	None
Ventrucci et al., [29]	Walker-256 tumor-bearing pregnant rats	Leucine	→ normal protein turnover	None
Salomão et al., [28]	Walker-256 tumor-bearing rats submitted or not to aerobic training	Leucine	→ normal protein turnover ↓ tumor growth	None
Peters et al., [26]	C26 tumor-bearing mice	Leucine	↓ Muscle loss	None
Patra et al., [14]	Sarcoma 180 tumor-bearing mice	Creatine	↑ anticancer effect of methylglyoxal	None
Human studies				
Tayek et al., [31]	Patients with intra-abdominal metastatic adenocarcinoma.	BCAA	↑ whole body protein synthesis ↔ 24-h nitrogen balance	None
Yamanaka et al., [32]	Gastric cancer patients	BCAA	→ normal protein turnover	None
Norman et al., [46]	Patients with colorectal cancer undergoing chemotherapy	Creatine	↑↔ body cell mass ↑ handgrip strength	None
Bourgeois et al., [13]	Children with acute lymphoblastic leukemia	Creatine	↔ bone mineral content and fat-free mass ↓ gain in body fat	None

5 Final considerations

BCAAs and creatine may attenuate proteolysis and enhance proteins synthesis in skeletal muscle. Although more experimental studies and clinical trials are still necessary to elucidate this therapeutic application, several evidences have demonstrated that amines supplementation is a promising coadjuvant treatment to cancer cachexia. Furthermore, the nutritional supplementation is a non-pharmacological strategy; hence, we also encourage the researchers to assess the safety of supplements in further studies underlying cancer cachexia.

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Disclosure of potential conflict of interest Patrícia Lopes de Campos-Ferraz, Isabel Andrade, Willian das Neves, Isabela Hangai, Christiano Robles Rodrigues Alves, and Antonio Herbert Lancha Junior declare that they have no conflict of interests.

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