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INVITED REVIEW

Branched-chain amino acids (BCAAs) as nutraceuticals for exercise

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ABSTRACT

Branched-chain amino acids (BCAAs: leucine, isoleucine and valine) are essential amino acids for humans and animals. It has been shown that BCAA oxidation is promoted by exercise through activation of branched-chain α-keto acid dehydrogenase complex (BCKDC), which is a rate-limiting enzyme in the catabolic pathway of the BCAAs, and the elevated enzyme activity in skeletal muscle is quickly downregulated after exercise. This tight regulation of the BCKDC is consistent with stimulation of protein synthesis after exercise in skeletal muscle. With this background, it is interesting to consider the BCAAs as a supplement for sports. We conducted a human study to examine the effects of BCAA supplementation on the delayed-onset muscle soreness (DOMS) induced by squatting exercises. The results clearly showed that BCAA supplementation significantly reduced DOMS evaluated by a visual analog scale method and maintained leg muscle force during the period of DOMS. Other studies using different types of exercise support our findings, suggesting that BCAA supplements are useful for conditioning of skeletal muscle after exercise.

Keywords: BCAA, exercises, DOMS, skeletal muscle

INTRODUCTION

Branched-chain amino acids (BCAAs: leucine, isoleucine and valine) are essential amino acids for humans and animals. BCAAs account for 35-40% of dietary essential amino acids in body proteins and 14-18% of the total amino acids in muscle proteins [1-4]. The muscle mass of humans is ~40% of the body weight; the muscle protein pool therefore represents a large reservoir of BCAAs in the body. In contrast, animals have a free amino acid pool, which appears to be constant [3], and the content of free BCAAs in the human skeletal muscle is < 0.1 g/kg muscle [2]. This pool of free BCAAs is extremely small compared to the BCAA content of muscle proteins. Recent studies have demonstrated that free BCAAs, especially leucine, play a very important role in protein metabolism; leucine promotes protein synthesis and inhibits protein degradation via mechanisms involving the mammalian target of rapamycin (mTOR) [5,6]. It has been shown that BCAA oxidation is promoted by exercise through activation of the branched-chain α-keto acid dehydrogenase (BCKDH) complex, which is a rate-limiting enzyme in the catabolic pathway of the BCAAs [7,8], and the elevated enzyme activity in skeletal muscle is quickly downregulated after exercise [9]. This tight regulation of the BCKDH complex is consistent with stimulation of protein synthesis after exercise [10,11]. These findings suggest that leucine is not only a building block of proteins but also a modulator of protein metabolism.

SPECIFIC FEATURES OF THE BCAA CATABOLIC PATHWAY

Disposal of BCAAs is conducted mainly in mitochondria. It involves reversible transamination to produce the corresponding branched-chain α-keto acids (BCKAs), which in turn are subjected to oxidative decarboxylation to produce CoA esters (Fig. 1). The enzymes that catalyze these two reactions are common to the three BCAAs.

The first enzyme in the catabolic pathway, branched-chain aminotransferase (BCAT), has two isozymes, the cytosolic type (BCATc) and the mitochondrial type (BCATm) [12], and

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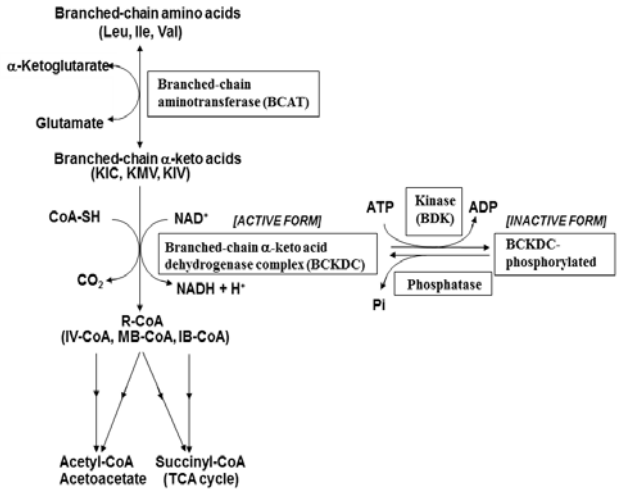

Fig. 1. Catabolism of branched-chain amino acids. KIC, a-ketoisocaproate; KMV, a-keto-ß-methylvalerate; KIV, a-ketoisovalerate; CoA-SH, coenzyme A, reduced form; R-CoA, acyl-CoA; IV-CoA, isovaleryl-CoA; MB-CoA, a-methylbutyryl-CoA; IB-CoA, isobutyryl-CoA; and BDK, branched-chain a-keto acid dehydrogenase kinase.

the latter is expressed in tissues throughout the body except for the liver. However, since BCATm has relatively high *K*m values (0.5-3 mM) for BCAAs compared to the BCAA concentration in tissues [13], this enzyme is not normally the most important regulator of BCAA catabolism. On the other hand, the second step enzyme, BCKDC, catalyzes an irreversible reaction that commits individual BCKAs to their respective degradation pathways [7]. Since BCAAs account for about 20% of our dietary protein and are essential for the synthesis of proteins, branched-chain fatty acids, and neurotransmitters, their catabolism must be tightly regulated. BCKDC is considered the most important regulatory enzyme in the catabolic pathways of the three BCAAs [14]. The complex consists of three catalytic components: a BCKA decarboxylase (E1), a dihydrolipoyl transacylase (E2), and a dihydrolipoyl dehydrogenase (E3). The activity of the complex is controlled by covalent modification in which phosphorylation of the E1 component by a specific kinase (branched-chain α-keto acid decarboxylase kinase (BDK)) inactivates [7] and dephosphorylation of the E1 component by a specific phosphatase reactivates the complex [15,16] (Fig. 1).

REGULATION OF BCAA CATABOLISM

Tight control of BCKDC activity is important for conserving as well as disposing of BCAAs. Commonly, phosphorylation of the complex occurs when there is a need to conserve BCAAs for protein synthesis, whereas dephosphorylation occurs when BCAAs are present in excess. A defect in BCKDC causes maple syrup urine disease (MSUD), a devastating condition that clearly shows the importance of disposing of excess BCAAs in the circulation. A mitochondrial protein kinase (BDK) that is specific to BCKDC has been isolated and characterized [17]. Evidence suggests that BDK is critically important in determining the activation state of BCKDC [7]. In addition, known mechanisms for short-term control of BCKDC activity include direct inhibition by NADH and CoA esters derived from the degradation of BCAAs. Activation of the complex can also be achieved in the short term by inhibition of BDK by α-ketoisocaproate, the product of leucine transamination. It has been demonstrated that ingestion of a large amount of leucine activates hepatic BCKDC and results in significant decreases in the concentration of isoleucine and valine in rats [18]. Compared to α -ketoisocaproate, the BCKAs from isoleucine and valine (α -keto-ß-methylvalerate and α-ketoisovalerate, respectively) are weaker inhibitors of BDK [19]. Therefore, ingestion of isoleucine or valine has less influence than leucine on the plasma concentration of the other BCAAs.

It has been shown that BDK exists in bound and free (unbound) forms [20]. The bound form of the kinase can be immunoprecipitated from extracts of rat liver mitochondria with antibodies against the E1 subunits of BCKDC. Supernatants produced by immunoprecipitation of E1 contain significant amounts of the kinase corresponding to its free form. Under most conditions, the amount of free BDK exceeds that of the kinase bound to the complex in rat liver mitochondrial extracts. In the routine method for measuring BDK activity in rat liver [21], BCKDC and BDK are co-precipitated with 9% polyethylene glycol (PEG) prior to the assay of kinase activity. Although free and bound BDK are both completely recovered in 9% PEG precipitates, kinase activity against the recovered BCKDC correlates with the amount of the bound form of the kinase rather than its total amount. Furthermore, we found that BDK inhibitors, such as α-ketoisocaproate (KIC) and α-chloroisocaproate, dissociated the bound form of BDK from BCKDC in a dose-dependent manner [22]. The amount of total kinase is little affected by acute changes in physiological conditions [14]. These findings suggest that the bound rather than the free form of BDK is responsible for phosphorylation and inactivation of the complex.

PROMOTION OF BCAA CATABOLISM BY EXERCISE

It is believed that BCAAs are oxidized mainly in skeletal muscle. BCAA oxidation in skeletal muscle is enhanced by

exercise, and activation of BCKDC in skeletal muscle is responsible for the enhanced BCAA oxidation (7, 8). Especially in rat skeletal muscle, almost all of the BCKDC is in an inactive (phosphorylated) state under sedentary conditions (23). We examined the mechanism responsible for activation of the complex in rat skeletal muscle by exercise using an electrically stimulated muscle contraction model (24). [[We found that increases in leucine and KIC concentrations in the muscle are suggested to be IS THIS A FINDING OR A SUGGESTION? IT CANNOT BE BOTH!]] one of the factors responsible for BCKDC activation in skeletal muscle, because KIC inactivates the kinase by dissociation of the kinase from the BCKDC (25).

SUPPRESSION OF DELAYED-ONSET MUSCLE SORENESS (DOMS) BY BCAA SUPPLEMENTATION

Since ingestion of BCAAs prior to exercise is suggested to decrease protein degradation in skeletal muscle [2,26], it is interesting to consider the effect of BCAA supplementation on exercise-induced DOMS. Therefore, we conducted an experiment to examine this hypothesis using young, healthy, untrained female subjects who performed squatting exercises (7 sets of 20 squats/set with 3 min intervals between sets) to induce DOMS [8,27]. The experiment was designed as a crossover double blind design. On the day of the exercise session, the subjects ingested either BCAAs (Ile:Leu:Val = 1:2.3:1.2) or dextrin at 100 mg/kg body weight as a test drink before the squatting exercises. DOMS peaked on days 2-3 in both trials, but the level of soreness was significantly lower in the BCAA arm than in the placebo arm. Leg muscle force during maximal voluntary isometric contractions that was measured on day 3 (during peak soreness) was decreased by 20% in the placebo trial, but not in the BCAA trial. Plasma BCAA concentrations, which were decreased after exercise in the placebo trial, were markedly elevated 0-2 h post-exercise in the BCAA trial. These results clearly indicate that DOMS induced by exercise is suppressed by BCAA supplementation. Our finding is supported by studies that examined the effects of BCAA supplementation on DOMS using other types of subjects and exercise [28-31].

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