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BRANCHED CHAIN AMINO ACIDS AND THEIR IMPORTANCE IN NUTRITION

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ABSTRACT

Branched chain amino acids (BCAA) - leucine, isoleucine and valine are essential amino acids which are metabolized directly in muscles and offer energy fuel to performance of the work. There is lot of evidences supporting the positive effect of BCAA supplementation on muscle growth. The main importance is attached particularly to leucine. There was observed that leucine supplementation increased protein synthesis in skeletal muscles after resistance exercise in young people and in elderly people suffered by sarcopenia as well. There is not exactly clear, what is the reason for the positive effect of BCAA to increase protein synthesis in muscles. Besides the positive effect of BCAA on muscle growth, there was observed their positive effect against fatigue and on a production of endogenous glucose, which is necessary to maintain the glucose balance in body during adaptation to stress. The minimum and maximum dose of BCAA is not established, but the daily recommended amount of leucine : isoleucine : valine is in a ratio 40:20:20 mg.kg body weight $^{-1}$. It is recommended to use the mixture of BCAA rather than leucine individual, because of depletion other BCAA in body. There was observed no toxicity of BCAA even at high doses. The present review describes the metabolism of action and effect of BCAA on protein synthesis and physiological functions in human.

Keywords: Branched chain amino acid; protein; leucine; isoleucine; valine

INTRODUCTION

Well balanced amino acids content of protein diet is necessary for lean muscle growth. Required amount of dietary protein is necessary for protein synthesis. Not only proteins but also amino acids, constituents that make up proteins, are important part of nutrition which could not be neglected, especially when resistance exercise is performed. Besides the supplementation of complex essential amino acids, that the body is not able to synthesize, supplementation of branched chain amino acids (BCAA) is important. Leucine, isoleucine and valine are of the same structure of branched chain and so they are known as branched chain amino acids - BCAA. They belong among essential amino acids for humans and animals and have common membrane transport systems and enzymes for their transamination and decarboxylation (**Harper *et al.*, 1984**). It indicates that they are closely connected with their metabolism in a body. BCCA represent 35 - 40 % of dietary essential amino acids in body proteins and 14-18 % of total amino acids present in muscle proteins (**Riazi *et al.*, 2003; Layman and Baum, 2004**).

Table 1 Content of BCAA in different foods, feeds and protein sources (g.kg^{-1} DM)*

	CP	Leu	Ile	Val	Total BCAA	BCAA expressed as % of CP	Ratio of Leu : Ile : Val
Foods and feeds							
Rye[1]	153.1	10.0	4.4	6.5	20.8	13.6	2 : 0.9 : 1.3
Barley[1]	141.3	9.1	4.3	6.2	19.6	13.9	2 : 0.9 : 1.4
Soybean meal[1]	490.2	39.8	21.5	24.0	85.3	17.4	2 : 1.1 : 1.2
Malting sprouts[1]	204.4	15.0	8.8	12.6	36.5	17.8	2 : 1.2 : 1.7
Sorghum[1]	105.1	15.1	4.9	6.3	26.3	25.0	2 : 0.6 : 0.8
Wheat germs[1]	201.3	21.4	11.8	17.4	50.6	25.1	2 : 1.1 : 1.6
Broken rice[1]	89.6	6.2	3.3	5.2	14.8	16.5	2 : 1.1 : 1.7
Protein sources							
Pea protein concentrate[2]	878.2	69.7	39.6	43.0	152.3	17.3	2 : 1.1 : 1.2
Soy protein concentrate[2]	703.8	55.7	32.3	33.9	121.9	17.3	2 : 1.2 : 1.2
Casein[2]	969.8	89.8	49.0	63.3	202.1	20.8	2 : 1.1 : 1.4
Whey protein concentrate[2]	808.5	89.3	50.2	48.1	187.6	23.2	2 : 1.1 : 1.1
Rice protein concentrate[3]	728.4	57.3	31.4	44.6	133.3	18.3	2 : 1.1 : 1.6

* BCAA - branched chain amino acids; CP – crude protein; Leu –leucine; Ile – isoleucine; Val – valine
[1] **Brestenský *et al.*, (2013),** [2] **NRC (2012),** [3] **Gottlob *et al.*, (2012)**

Human musculature represents 40 % of total body weight of a man, and so muscle proteins "pool" represents very large reservoir of BCAA in the body. But the content of free BCAA in skeletal muscle of human is low; only 0.1 g (0.6-1.2 mmol)/muscle kg (**Rennie, 1996**). Total concentration of BCAA in human blood (0.3-0.4 mmol/l) is relatively high when compared with other amino acids (except for glutamine) (**Ahlborg *et al.*, 1974; Wahren *et al.*, 1976**). However, in comparison with content of BCAA in muscle, total amount of BCAA in human blood is low.

Content of individual and total BCAA among various feeds and protein sources is different (**Table 1**). The higher content is in protein sources compared to foods and feeds. Leucine content is between 41 - 58 % of total BCAA and the ratio of leucine : isoleucine : valine is similar within the foods and protein sources as well, but is not completely identical to recommended ratio 2:1:1 (**Kurpad *et al.*, 2006**), and is slightly higher, regarding isoleucine and valine. The content of BCAA corresponds to the content of crude protein (**Fig. 1**).

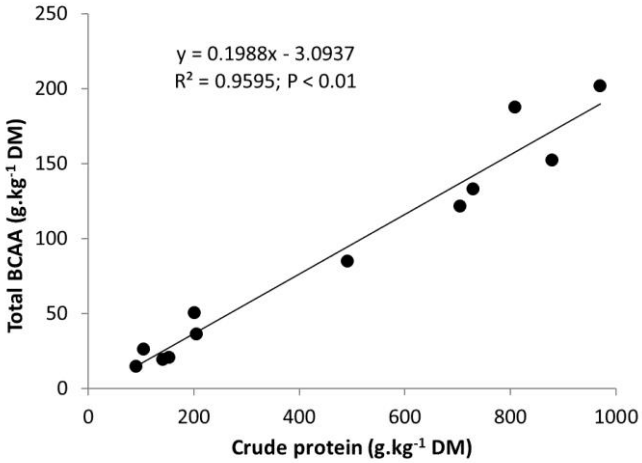

Figure 1 The ratio of total content BCAA to crude protein in foods, feeds and protein sources

BCAA metabolism in the body

In contrast to other amino acids, BCAA are metabolized directly in the muscles and their catabolic pathways are located in the mitochondria. The first step in BCAA metabolism in tissues is production of branched chain keto acids that are incorporated into proteins or circulate in the body and serve as an energy substrate for skeletal muscle, brain, liver and heart **(Abumrad *et al.*, 2001**). Branched chain amino acid aminotransferase (BCAT) enzyme is responsible for change of BCAA into keto acids. Another enzyme - branched-chain α-keto acid dehydrogenase (BCKDH) causes decarboxylation of keto acids in the tissues and organs with generation of substrates entering the citrate cycle **(Darner and Elsas, 1989).** BCAA catabolism is carried out in two steps (**Fig. 2**): 1) reversible transamination of α-keto acids in presence of BCAT **(Bixel *et al.*, 1997)**; 2); the second step is catalyzed by BCKDH and it is irreversible **(Harris *et al.*, 1997)**. Alpha-keto acids generated during this step are subject to oxidative decarboxylation from which derivatives of coenzyme A are generated **(Platell *et al.*, 2000)**. Intensity of BCAA oxidation is different in individual tissues and it depends on the activity of transaminase and dehydrogenase. BCKDH exists both in active form (dephosphorylated) and in non-active form (phosphorylated). Enzyme that is responsible for activation and inactivation of BCKDH is BCKDH-kinase which occurs particularly in mitochondria **(Anderson and Hanson, 1983; Harris *et al.*, 1997)**. BCKDH is activated during training by dephosphorylation of BCKDH-kinase. It was found that activity of BCKDH in the muscles is increased 10-times during training **(Kasperek *et al.*, 1985)**. Increased activity of BCKDH was also observed during starvation **(Kasparek, 1989).** Dephosphorylation is connected with decrease of ATP level in the muscles (**Shimomura *et al.*, 1995**). BCAT concentrations are the highest in the skeletal muscle, and so muscles are the main place of BCAA transamination **(Harper *et al.*, 1984)**. During increased physical activity or during the stress and infection periods (when there is increased consumption and lack of energy in the body), BCAA metabolism in the skeletal muscle is increased. When catabolism of proteins is increased, flow of BCAA is also increased.

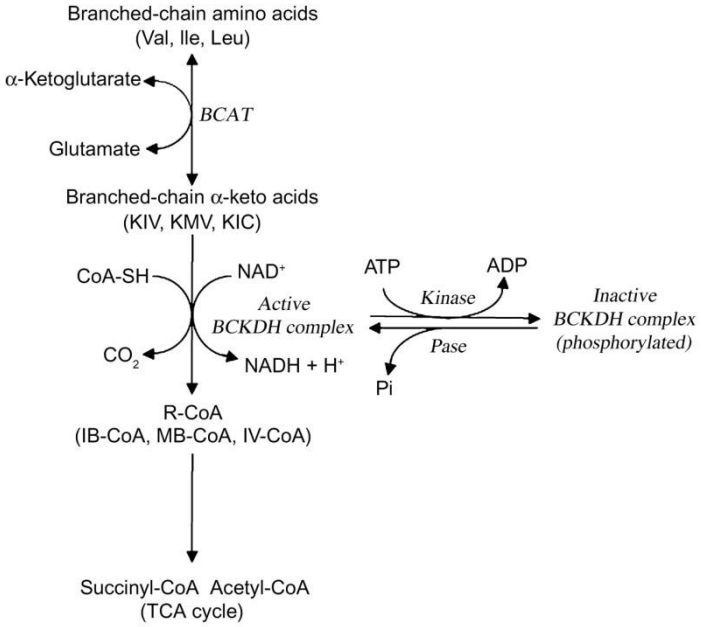

Figure 2 Degradation pathway for branched-chain amino acids (BCAA); BCAT: branched-chain amino acid transaminase; BCKDH: branched-chain α-keto acid dehydrogenase; KIV: α-ketoisovalerate; KMV: α- keto-beta-mehylvalerate; KIC: α-ketoisocaproate; CoA-SH: coenzyme A reduced form; IV-CoA: isovaleryl CoA; R-CoA: acyl CoA; Pase: phosphatase **(Shimomura *et al.*, 2004)**.

Catabolic state of the body and BCAA

Catabolic state of the body is characterized by increased proteolysis, gluconeogenesis, decreased proteosynthesis and negative nitrogen balance. These states can be observed most often during infections, diseases and nutritional deficiencies. Therefore, it is very important to protect muscle mass during catabolic states, particularly during periods with increased occurrence of infections.

BCAA oxidation is increased during catabolic state of the body. In this time, BCAA represent important source of energy for skeletal muscle (**Platell *et al.*, 2000**). Changes in BCAA metabolism during catabolic states are influenced by long-term activity of BCKDH (**Garcia-Martinez *et al.*, 1985**) what explains increased oxidation of BCAA. Several studies reported that administration of BCAA to people in catabolic states (postoperative, multiple trauma, severe burns and sepsis) improved nitrogen balance, increased concentration of amino acids in the plasma, increased protein synthesis and decreased catabolism in the skeletal muscle (**Echenique *et al.*, 1984**). Based on this information it is evident that BCAA protect muscles when the body is in catabolic state caused by insufficient nutrition or diseases.

Fatigue and brain function

It is assumed that BCAA concentration in plasma affects brain functions, appetite, as well as physical and mental fatigue. BCAA influence brain functions by changing of utilization of the aromatic amino acids. Leucine, isoleucine and valine directly or indirectly participate on different bio-chemical reactions in the brain **(Fernstrom, 1990)**, such as protein synthesis, energy production, compartmentalization of glutamate, neurotrasmitter serotonin synthesis **(Suryawan *et al.*, 1998; Daikhin and Yudkoff, 2000)**.

BCAA are transferred by blood to the brain via blood brain barrier transport system and they are the main source of nitrogen for production of glutamate and glutamine in the brain **(Chuang *et al.*, 1995)** and serve as energy substrate for the brain. They are swiftly metabolized in the neurons also despite the fact that there is sufficient amount of other energy substrates, such as glucose. BCAA and particularly leucine provide amino group necessary for glutamate synthesis **(Kanamori *et al.*, 1998; Hutson *et al.*, 2001)** and they are a source of nitrogen for peripheral tissues in the amount of 30-50 % **(Yudkoff *et al.*, 2005)**. Leucine crosses rapidly into the brain, first passing into astrocytes, where it is swiftly transaminated. Glutamate and branched chain keto acids are products of transamination, and keto isocapronate (KIC) is a product of leucine **(Fig. 2)**. Glutamate is neurotransmitter which acts as a stimulator that increases neuron activity in the brain. The brain can oxidize KIC and leucine to CO_2 **(Auestad *et al.*, 1991)**, but degree of this oxidation is lower than the degree of transamination **(Shambaugh and Koehler, 1983)**.

Blood brain barrier transport system is the same for both BCAA and tryptophan. Since this transport system has limited capacity, BCAA and tryptophan compete to transfer also through this transport system. When BCAA concentration in the blood increases, transport of tryptophan to the brain is decreased **(Fernstrom**

2005). Due to the fact that tryptophan is metabolized in the brain to 5 hydroxytryptamine (5-HT; serotonin), reduced transfer of tryptophan into the brain will result to reduce the amount of metabolized 5-HT, which has slightly sedative effects and is responsible for fatigue (**Struder *et al.*, 1998; Blomstrand, 2006**).

Increased BCAA concentrations in the blood suppress fatigue by blocking the entry of tryptophan into the brain. This is also confirmed by several works dealing with effect of BCAA on fatigue. When a mixture of BCAA was administered to people during training, they stated reduction of exertion and mental fatigue (**Blomstrand *et al.*, 1997**). Similarly, also physical performance measured as a time to exhaustion was improved from 137 minutes to 153 minutes. (**Mittleman *et al.*, 1998**).

BCAA and glucose metabolism

Due to increased degradation of BCAA in peripheral tissues, increasing the concentration of BCAA occurs in cells. Decomposition of BCAA in the skeletal muscle results in increased production of alanine and glutamine and maintenance of glucose equilibrium in the body (**Layman 2003**). The relationship between BCAA and the glucose level is related to glucose-alanine cycle (**Ahlborg *et al.*, 1974**), within which BCAA are released from the liver. Subsequently, released BCAA are transmitted by blood to the muscles. Uptake of BCAA in the skeletal muscles increases concentration and transamination of BCAA in the cells and incorporation of amino nitrogen into pyruvate from which alanine is produced. Alanine is transmitted from the muscles to the liver by blood, where it is changed to pyruvate from which glucose is produced. Amino acids serve as a primary source of carbon necessary for gluconeogenesis (**Jungas *et al.*, 1992**). Production of endogenous glucose is a crucial factor for maintaining the balance of glucose in the body (**Balasubramanyam *et al.*, 1999**). BCAA provide 25-30 % of nitrogen necessary for formation of alanine (**Haymond *et al.*, 1978**), from which glucose is produced. Glucose is important in the process of adaptation to stress and starvation.

BCAA and protein metabolism

Recent studies showed that free BCAA, particularly leucine, play important role in protein metabolism. Leucine stimulates protein synthesis and prevents breakdown of proteins by a mechanism containing so called mammalian target of rapamycin - mTOR (serine - threonine - protein kinase regulating growth, proliferation, motility, and survival of cells and synthesis and transcription of proteins) (**Mordier *et al.*, 2000; Bolster *et al.*, 2004**). Leucine is not only a structural part of proteins, but it also forms protein metabolism. BCAA are metabolized out of liver in the skeletal muscle (**Buse and Reid, 1975; Shinnick and Harper, 1976**). They are important source of energy in the muscles during training and in stress periods, as well as precursors of other amino acids and proteins (**Ferrando *et al.*, 1995**). The main source of energy for muscles is oxidation of BCAA (**Shinnick and Harper, 1976; Harper *et al.*, 1984**). The oxidation is controlled by by-products of leucine transamination for short time (**Parker and Randle, 1978**) and by many physiological and pathological conditions for long time period, such as starvation, diabetes, inflammation processes, cancer illnesses and infections (**Harris *et al.*, 1985; Argiles and Lopez-Soriano, 1990; Nawabi *et al.*, 1990; Hayashi *et al.*, 1996; Lombardo *et al.*, 1998; Price *et al.*, 1998**).

Moreover, BCAA significantly affect glutamine metabolism (**Darmaun and Dechelotte, 1991**). Glutamine is important nutrient for rapidly growing cells in the body, particularly in intestine and immune system. BCAA are transferred from food through the liver to the system circulation of the body, where more than 60 % of them are processed by metabolism in the muscles (**Gelfand *et al.*, 1986**). They are used as oxidative source of energy in the muscles. They stimulate glutamine and alanine synthesis, which are exported to the liver. Here, they form glucose that is a source of energy. There is so called liver-muscle metabolic pathway in the body. This pathway is particularly important during starvation, because alanine, which is synthesized in the muscles *de novo*, becomes a main precursor for the liver gluconeogenesis. Alanine carbon is mostly created by BCAA, particularly by valine **(Freund *et al.*, 1979**).

Increased availability of amino acids and resistance training directly increase synthesis of proteins in the skeleton musculature. BCAA, particularly leucine, have anabolic effect on protein metabolism in such a way that they increase degree of protein synthesis and decrease degree of proteolysis in the skeletal musculature of people staying in rest (**Louard *et al.*, 1990; Nair *et al.*, 1992**). BCAA have anabolic effect in the skeletal muscle also during recovery period after the training (**Blomstrand and Saltin, 2001**). The administration of BCAA increases phosphorylation of proteins that participate on regulation of protein synthesis, including p70S6K in human skeletal musculature (**Liu *et al.*, 2001**). The p70S6k a serine threonine kinase is an enzyme, which goal is S6 ribosome protein. Its phosphorylation indicates protein synthesis in ribosome. The p70S6k activity induced by training correlates with growth of skeletal musculature observed after six weeks of resistance training and with increased degree of protein synthesis (**Baar and Esser, 1999**). Changes in p70S6k phosphorylation in skeletal musculature after the training can reflect activation of so called signal pathways that can be responsible for growth of protein synthesis during early recovery period after the training. It is assumed that BCAA increase protein synthesis in the skeletal musculature during recovery after resistance training by p70S6k signaling cascade (**Karlsson *et al.*, 2004**).

Resistance training increases musculature due to higher degree of protein synthesis compared to protein breakdown, but the net protein increase was achieved only in combination with a nutritional supplement (**Biolo *et al.*, 1997; Tipton *et al.*, 1999**). Synthesis of myofibril proteins increases, and because these proteins form 80 % of skeletal proteins, the effect of resistance training can be measured as an increase of muscles volume or a cross-section of muscle fiber after the training (**Tesch, 1988**).

Importance of leucine for protein synthesis

Studies carried out with people in rest showed that the BCAA administration, particularly leucine, has anabolic effect on protein metabolism what is reflected either with increased protein synthesis or decreased protein breakdown (**Alvestrand *et al.*, 1990; Louard *et al.*, 1990; Nair *et al.*, 1992**). In spite of the fact that relatively quick response on increase of efficiency of amino acids in the body was observed, time necessary for stimulation effect of the amino acids on protein metabolism is not known (**Bohé *et al.*, 2001**). The BCAA mixture infusion stimulated the protein synthesis for 30 minutes after the infusion and it also increased the degree of synthesis for another 90 minutes (**Bohé *et al.*, 2001**). The infusion of BCAA or pure leucine increased phosphorylation of p70S6k kinase and 4E-BP1 in the skeletal musculature for 2 to 6 hours (**Greiwe *et al.*, 2001; Liu *et al.*, 2001**). Increase of phosphorylation of p70S6k kinase was confirmed 6 hours after taking the infusion consisting of amino acids mixture.

In relation to resistance training, intake of amino acids or protein hydrolyzate after the training stimulates the degree of protein synthesis in the muscles and causes positive nitrogen balance (degree of protein synthesis is higher than degree of protein breakdown) (**Rasmussen *et al.*, 2000; Børsheim *et al.*, 2002; Tipton *et al.*, 2004**). There are different theories explaining this effect: 1) Increased efficiency of amino acids increases their transport to the muscles. It is assumed that it stimulates degree of protein synthesis in the muscles (**Wolfe, 2001**), 2) Another possibility is that the stimulation effect of one amino acid or a group of several amino acids occurs, e.g. BCAA - particularly leucine. High concentrations of leucine are related to protein synthesis of proteins (**Ferrando *et al.*, 1995; Louard *et al.*, 1995**). Approximately 40 % of leucine transported to muscles passes to amino acids pool, 40 % is oxidized and 20 % of leucine becomes part of proteins (**Alvestrand *et al.*, 1990**). An addition of leucine to protein hydrolyzate leads to higher stimulation of protein synthesis after the resistance training, in comparison if only hydrolyzate without addition of leucine is used (**Koopman *et al.*, 2005**). It is documented that leucine causes release of insulin from the pancreas and it is assumed that the anabolic effect of leucine is connected with insulin. When BCAA had been administered during endurance training (running, cycling), their positive effect was observed during the recovery period, as well as during the training (**Blomstrand and Newsholme, 1992; Blomstrand and Saltin, 2001**).

Moreover, leucine as the main regulator of protein synthesis in the muscles plays an important role in reduction of sarcopenia - loss of muscle mass associated with aging. With aging, the muscles do not response to anabolic effect of amino acids (**Cuthbertson *et al.*, 2005**) and antiproteolytic effect of insulin (**Wilkes *et al.*, 2009**) and the degree of protein synthesis in muscles is decreased. Studies carried out on rats (**Rieu *et al.*, 2003**) and men (**Kastanos *et al.*, 2006; Rieu *et al.*, 2006**) showed that leucine is able to restore the degree of protein synthesis in old muscles. In case of consumption of essential amino acids in the amount of 6.7 g (of which 26 % is leucine) the degree of protein synthesis in the muscles of elderly people was not increased; it was increased only in the muscles of young people. But after increasing the content of leucine to 41 %, the degree of protein synthesis in the muscles was equally increased both in case of young and old people (**Katsanos *et al.*, 2006**). This effect was not observed, when the leucine was consumed together with common meal. When the leucine is administered separately in the form of a dietary supplement, a level of other BCAA in plasma can be depleted (**Dardevet *et al.*, 2000**). Therefore, more efficient and suitable is to use balanced mixtures of BCAA than free leucine (**Balage and Dardevet, 2010**). Supplementation by leucine is more effective, when it is combined with resistance training, because synthesis of myofibril proteins is stimulated after the training. Beside this fact, both forms - either training or nutrition are effective strategies for increasing of muscle mass of elderly people (**Churchward-Venne *et al.*, 2012**). There is not well established daily recommended dose of BCAA, but only mutual ratio of leucine : isoleucine : valine, in proportion of 2:1:1. Some studies recommended dose of leucine : isoleucine : valine in a daily amount of 40: 17-20 : 20 mg.kg body weight $^{-1}$ (**Kurpad *et al.*, 2006**), but some studies reported beneficial effect of BCAA at minimum dose in a daily amount higher than 5 g (**Shimomura *et al.*, 2004**). Despite this fact, **EFSA (2012)** reported that there is no evidence that leucine supplementation in daily dose higher than 39 mg.kg body weight^{-1}, would be effective in promoting of muscle growth. Supplementation of BCAA is safe. In animal studies, there was demonstrated no toxicity even at doses exceeding 10 g.kg body weight $^{-1}$ (**Okazaki *et al.*, 1989**).

CONCLUSION

It was well documented the positive effect of BCAA supplementation to the diets on protein synthesis. Especially when resistance training is performed, in order to stimulate muscle growth, BCAA play important role as an energy fuel and constituent stimulating protein synthesis. More over BCAA have positive effect against sarcopenia in elderly people. Based on this information, BCAA supplements are important part of protein nutrition but minimal dose for their beneficial effect is not clearly established. In conclusion, it is necessary to note that to achieve positive effect of BCAA on muscle mass formation of people taking BCAA mixtures, these people should also take sufficient amount of other, particularly essential amino acids, especially in the form of different proteins directly from meal or in the form of dietary supplements.

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