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Effects of Oral Branched-Chain Amino Acids on Hepatic Encephalopathy and Outcome in Patients With Liver Cirrhosis

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Abstract

Branched-chain amino acids (BCAAs) constituting of valine, leucine, and isoleucine act as both substrates of proteins and as key regulators for various nutrient metabolisms. Patients with liver cirrhosis frequently lack sufficient BCAAs and therefore suffer from various metabolic disorders. Hepatic encephalopathy (HE) is a severe metabolic disorder with neurologic manifestations such as flapping tremors and coma in patients with liver cirrhosis. In addition, a mild form of HE known as minimal HE (MHE) is an important social issue because it occurs in up to 80% of patients with chronic liver disease and affects prognosis and activities of daily living, possibly resulting in falls and motor vehicle accidents. Although HE/MHE can be caused by various pathological conditions, including in an accumulation of mercaptans, short-chain fatty acids, and alterations in the gut flora, hyperammonemia has also been implicated in an important pathogenesis of HE/MHE. Besides urea cycle of liver, ammonia can be detoxified in the skeletal muscles by the amidation process for glutamine synthesis using BCAAs. Thus, BCAA supplementation may enhance detoxification of ammonia in skeletal muscle and may be a possible therapeutic strategy for HE/MHE. In this review, we summarize the clinical impacts of BCAA supplementation on HE/MHE and discuss possible mechanisms for a BCAA-induced improvement of HE/MHE. Furthermore, we present some modifications of oral BCAA therapy for improvement of efficacy in HE treatment. We also briefly describe pleiotropic benefits of BCAAs on life-threatening events and overall prognosis in patients with liver cirrhosis. *(Nutr Clin Pract.* 2013;28:580-588)

Keywords

nutrition therapy; ammonia; hepatic encephalopathy; cognitive impairment; branched chain amino acids; liver diseases; end-stage liver disease

Introduction

The amino acid valine, leucine, and isoleucine are known as branched-chain amino acids (BCAAs) because of their structural features. They are the most abundant essential amino acids, comprising approximately 40%. BCAAs serve as substrates for the synthesis of body proteins similar to the other amino acids. In addition, BCAAs are known to regulate various nutrient metabolism pathways.[1-6]

BCAAs have been suggested to be associated with the development of hepatic encephalopathy through alteration in ammonia and energy metabolisms. BCAAs are first catabolized, mostly in skeletal muscles, via BCAA aminotransferase (BCAT) with α-ketoglutarate into glutamate and branched-chain keto acids (BCKAs).[7-9] Although glutamate forms alanine in the presence of pyruvate and alanine aminotransferase, it also forms glutamine via glutamine synthetase (GS) and detoxifies ammonia when there are increased levels of ammonia (Figure 1), contributing to the improvement of hyperammonemia and hepatic encephalopathy.[7-9] The other metabolites of the reaction, BCKAs, then undergo oxidative decarboxylation, catalyzed by BCKA dehydrogenase (BCKDH), to form the corresponding branched-chain acylcoenzyme A (acyl-CoA) esters.[7-9] Then, branched-chain acyl-CoA is metabolized in the tricarboxylic acid (TCA) cycle, resulting in energy production. The energy production occurs in neurons and astrocytes, contributing to the improvement of cerebral activity and hepatic encephalopathy (Figure 1).[7-9]

Recently, BCAAs have been investigated as pharmacological agents.[1,3-6] BCAAs, particularly Leu, activate the mammalian target of rapamycin and subsequently upregulates the downstream eukaryotic initiation factor 4E-binding protein-1 and 70-kDa ribosomal protein S6 kinase, which regulate mRNA translation and synthesis of protein.[1,10-12] BCAAs also

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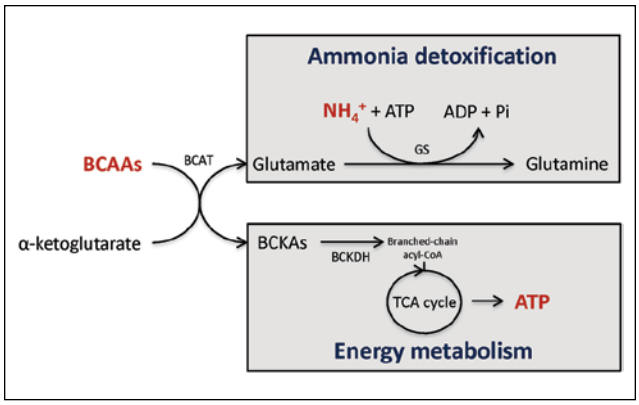

Figure 1. The metabolism of BCAAs in the skeletal muscle. BCAAs, branched-chain amino acids; BCAT, BCAA aminotransferase; NH_4^+, ammonia; ATP, adenosine 5'-triphosphate; ADP, adenosine 5'-diphosphate; BCKAs, branched-chain keto acids; BCKDH, BCKA dehydrogenase; Acyl-CoA, acylcoenzyme A esters; TCA, tricarboxylic acid.

upregulate both intracellular insulin signaling molecules including phosphatidylinositol 3-kinase and liver X receptor α/sterol regulatory element binding protein-1c pathway, resulting in improvement of glucose metabolism/insulin resistance.[1,13-17] They also control food intake or energy balance via action on central nervous system.[18-20] In particular, on the protein metabolism, leucine among the BCAAs seems to play an important role in the protein synthesis in several tissues including the liver, skeletal muscle, and adipose tissue.[21-23] Furthermore, leucine and isoleucine seem to be associated with glucose metabolism in the liver and skeletal muscle.[24-26] Thus, BCAAs exert various effects on nutrient metabolisms.

Metabolic disturbances in carbohydrates, lipids, or amino acids and proteins pathways, such as hepatic encephalopathy (HE), are evident in patients with liver disease.[27-29] Because the serum level of BCAAs, along with BCAA-to-aromatic amino acid (AAA) ratio, decreases in these patients, supplementation of BCAAs is an attractive potential treatment strategy to improve these metabolic disturbances. In this review, we describe the impact of BCAAs on the prevention and treatment of HE. In addition, we briefly summarize pleiotropic benefits of BCAAs for cirrhotic patients.

Diagnosis of HE

HE is a common complication of fulminant hepatitis or cirrhosis, characterized by various neurological manifestations. Therefore, HE is generally diagnosed by the presence of a depressed level of consciousness and neurological abnormalities after the exclusion of the other brain diseases. Recently, a new nomenclature of HE was proposed on the basis of the type of hepatic abnormality and the duration or characteristics of neurologic manifestations.[30] Three types of hepatic abnormalities are associated with HE.[30] Episodic HE is characterized by the HE between the HE episodes, whereas persistent HE is characterized by the lack of quiescent HE. Minimal HE (MHE) is defined as HE remaining below the clinically detectable levels.[31-33]

The severity of HE is subjectively assessed because of the absence of objective criteria. The West-Haven criteria are most widely used for grading the severity of HE.[30] Grades 2 to 4 of HE can be simply and clinically diagnosed because the presence of neurologic manifestations is overt, whereas grade 1 of HE is usually diagnosed retrospectively because no specific signs and symptoms pertaining specifically to grade 1 of HE exist. Therefore, it is clinically difficult to distinguish grade 1 of HE from a normal state (grade 0). Furthermore, MHE could be latent in grade 0 because MHE is defined as cognitive dysfunction without clinical signs of overt HE. Hence, clinical distinction among normal, MHE, and grade 1 of HE is difficult.

MHE is usually diagnosed by neuropsychological tests with at least 2 of the following neuropsychological tests:[30] a battery using number connection test (NCT) A and B, blockdesign test, and digit-symbol test or a standardized test battery including NCT A and B, line-tracing test, serial-dotting test, and digit-symbol test (PSE-Syndrome-Test). Although equipment is required, quantitative neurophysiological tools such as electroencephalography with mean dominant frequency, P300 auditory evoked potentials are also recommended.[30,34-40]

Effects of Oral BCAAs on HE

HE can be caused by various pathological conditions, including dehydration, spontaneous bacterial peritonitis, noncompliance of medication, an accumulation of mercaptans, short-chain fatty acids, γ-aminobutyric acid, benzodiazepines, and alterations in the gut flora, blood brain barrier, and regional differences in cerebral glucose metabolism.[41-50] In addition, a decrease in serum BCAA levels has been implicated in one of the pathogenesis of HE in cirrhotic patients.[5,51-53] Although lactulose or antibiotics are established treatment for HE, BCAA supplementation seems to further ameliorate HE in cirrhotic patients.

Although BCAAs are currently prescribed as an oral preparation,[54] the effects of oral BCAA supplementation on HE remain controversial, as summarized in Table 1. Four randomized controlled trials demonstrated that oral BCAA supplementation does not have beneficial effects on HE;[55-57] however, the number of enrolled patients in the BCAA arm of these studies is small ($n < 10$), and therefore these studies did not detect a difference between BCAA-treated and control groups. In fact, Ichida et al performed a multicenter study, enrolling a large number of cirrhotic patients ($n = 96$) to evaluate the efficacy of long-term administration of oral BCAA supplementation.[58] The study demonstrated that BCAA supplementation significantly increases BCAA-to-AAA ratio and decreases the hepatic encephalopathic grade.[58] In addition, Horst et al conducted a randomized study comparing dietary protein with an

Table 1. Randomized Control Trials of Oral BCAA Supplementation on HE in Cirrhotic Patients.

Reference	n	Control	Dose of BCAAs or Control	Trial period	Improvement of HE
Sieg et al[57]	14	Carbohydrate	13.2 g/day	3 months	No
Horst et al[59]	37	Dietary protein	20-60 g/day	4 weeks	Yes
Marchesini et al[60]	34	Casein	0.24 g/kg/day	3 months	Yes
Bianchi et al[61]	49	Casein	0.24 g/kg/day	3 months	Yes

BCAAs, branched-chain amino acids; HE, hepatic encephalopathy.

Table 2. Randomized Control Trials of Oral BCAA Supplementation on MHE in Cirrhotic Patients.

Reference	n	Control	Dose of BCAAs	Trial Period	Improvement of MHE
Plauth et al[63]	17	No amino acids	3 g/day	8 weeks	Yes
Les et al[64]	116	Maltodextrin	30 g/day/day	56 weeks	Yes

BCAAs, branched-chain amino acids; MHE, minimal hepatic encephalopathy.

oral BCAA supplement and showed a significant improvement in the mental status grade, flapping tremors, and portal-systemic encephalopathy index.[59] Similarly, 2 randomized double-blind casein-controlled trials conducted by Marchesini et al and Bianchi et al demonstrated that oral BCAA supplementation improves both nutrition parameters and the mental state of cirrhotic patients with chronic encephalopathy.[60,61] Therefore, oral administration of BCAAs may have beneficial effects on HE.

Effects of BCAAs on MHE

MHE, which is known as a subclinical or latent HE, is considered as the mildest form of the clinical spectrum of HE.[31,32] Kato et al demonstrated that nutrition consultations for energy and protein intakes improve MHE, and the severity of MHE is negatively associated with serum BCAA levels.[62] Thus, BCAA supplementation is considered as a therapeutic agent for MHE. In fact, 2 randomized controlled trials conducted Egberts et al and Plauth et al examined the effects of oral BCAA supplementation on MHE (Table 2) and showed that BCAA supplementation improves psychomotor functions, attention, practical intelligence, and automobile driving capacity.[63] Recently, Les et al conducted a randomized control trial to investigate the long-term effects of BCAA supplementation on the recurrence of HE[64] (Table 2). Although BCAA does not decrease the recurrence rate of HE in the study, BCAA improves MHE, evaluated by Trail Making Test part A, Digit Symbol Test, and Grooved Pegboard Test.[64] Thus, all of these randomized control trials corroborated the beneficial effects of BCAA supplementation in MHE. Since MHE occurs in up to 80% of patients with chronic liver disease[65] and affects daily living, possibly leading to falls, motor vehicle accidents, and prognosis,[38,39,65] BCAA supplementation may improve both MHE and the quality of life or prognosis in a great number of cirrhotic patients.

Mechanisms for BCAA-Caused Improvement of HE

Although the precise mechanisms for BCAA-caused improvement of HE remains unknown, several potential mechanisms are proposed (Figure 2). First, BCAAs enhance detoxification of blood ammonia in skeletal muscles.[66] In cirrhotic patients, increased blood ammonia is detoxified both in the liver and in the skeletal muscles, which is caused by liver dysfunction.[67] In skeletal muscles, BCAAs are catabolized to glutamate, which incorporates ammonia in the amidation process for glutamine synthesis, leading to a decrease in blood ammonia levels.[68] Thus, the skeletal muscle stimulatory effect and its potential role in ameliorating HE is being increasingly recognized. Second, BCAAs improve cerebral hyperammonemia.[69] Cerebral hyperammonemia causes impairment of neurotransmission and depletion of cerebral energy production as well as astrocyte swelling, leading to HE.[70] In both neurons and astrocytes, isoleucine is metabolized to acetyl-CoA and succinyl-CoA, which produce adenosine triphosphate (ATP) by enhancing TCA cycle metabolism and is subsequently metabolized to glutamate and aspartate. These amino acids serve as anaplerotic substances for the detoxification of cerebral ammonia. Third, BCAAs reduce brain uptake of AAAs and serotonin-precursor tryptophan. AAAs alter intracerebral synthesis of serotonin and produce octopamine and phenylethylamine, which act as false neurotransmitters, leading to HE.[71] BCAAs compete with AAAs and tryptophan for the amino acid transporter across the blood-brain barrier.[72] In addition to these favorable effects, BCAAs are known to promote liver

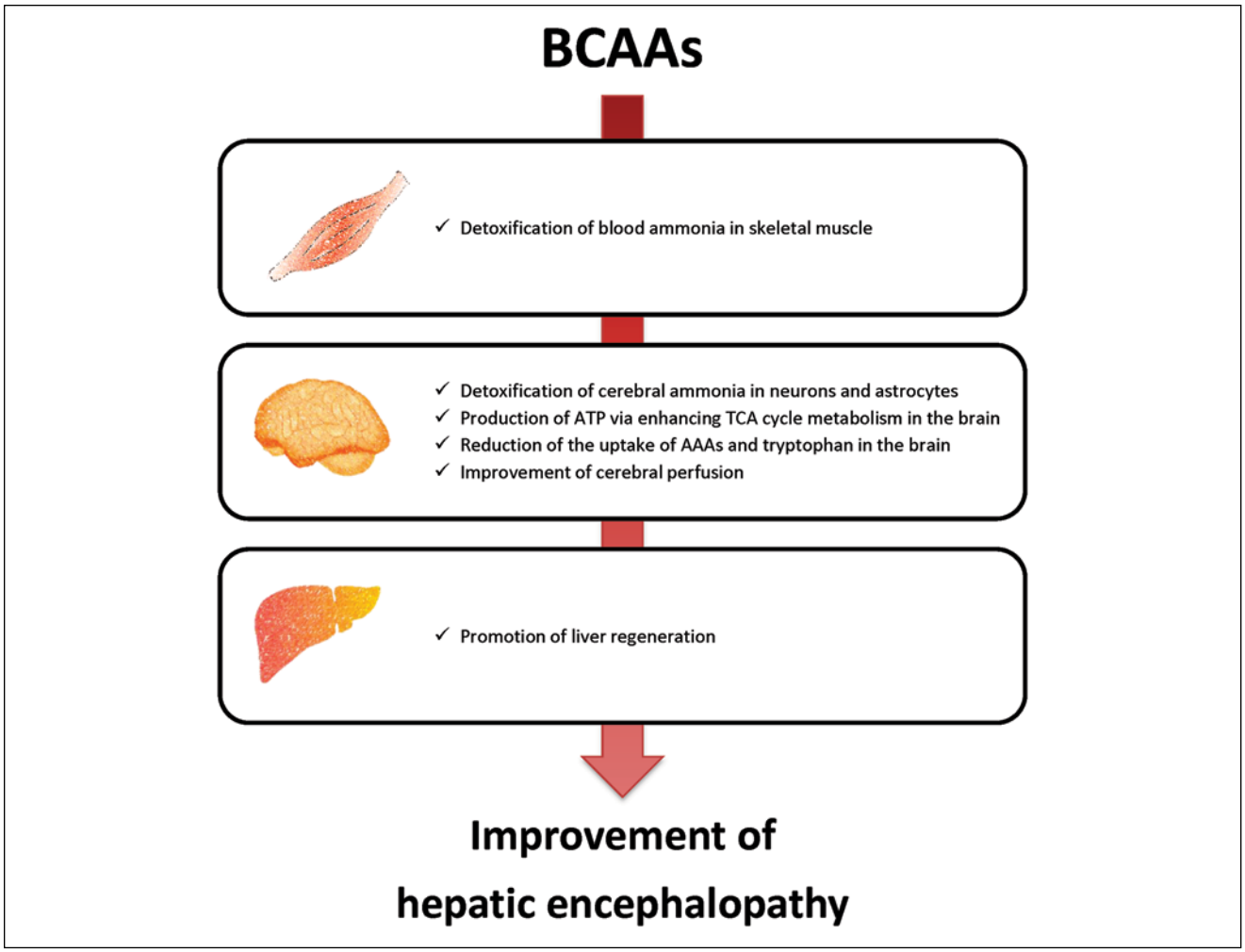

Figure 2. Mechanisms for BCAA-caused improvement of HE. BCAAs, branched-chain amino acids; ATP, adenosine 5'-triphosphate; TCA, tricarboxylic acid.

regeneration[73,74] and improve cerebral perfusion in patients with cirrhosis.[75-76] These effects may also be involved in the BCAA-induced improvement of HE.

Additive Effects of Zinc and Amino Acids to Oral BCAA Supplementation on HE

Zinc is a coenzyme of ornithine transcarbamylase (OTC), which is a key enzyme in the urea cycle of the liver.[77] Since cirrhotic patients are deficient in zinc, OTC activity is decreased, resulting in an increase of blood ammonia levels through the down-regulation of urea cycle.[78,79] In cirrhotic rats, oral zinc supplementation increased hepatic OTC activity, leading to a decrease in blood ammonia levels.[80,81] In cirrhotic patients, BCAAs in combination with zinc administration significantly decreased blood ammonia levels and improved HE compared to BCAA supplementation alone.[82,83]

The additive effects of other amino acids to oral BCAA supplementation have recently been investigated. Ndraha et al performed a randomized controlled, double-blinded study and demonstrated that the addition of $_{L}$-ornithine $_{L}$–aspartate (LOLA) to BCAA supplementation enhances the improvement of HE.[84] A possible mechanism is that LOLA stimulates the urea cycle and glutamine synthesis, which enhances the detoxification of ammonia.[85] Malaguarnera et al showed that the addition of $_{L}$-acetylcarnitine to BCAA supplementation significantly improves HE and decreases blood ammonia levels in a randomized controlled double-blind study.[86]

Other Favorable Effects of BCAAs

BCAA supplementation was originally invented in order to improve the imbalance of amino acids and nutrition status. However, recent studies have revealed that BCAAs modulate

Table 3. Pleiotropic Effects of BCAAs.

Effects	Number of Studies	References
Enhancement of albumin synthesis	19	4,16,90-103
Suppression of the development of HCC	16	104-119
Improvement of glucose metabolism/insulin resistance	12	16,17,107,120-128
Enhancement of immunity	7	129-135
Enhancement of liver regeneration	6	73,136-140
Suppression of tumor-associated angiogenesis	4	107,111,115,141
Suppression of hepatic fibrosis	3	90,142,143
Suppression of oxidative stress	2	144,145
Suppression of HCV replication	2	146,147
Improvement of QOL	5	4,74,148-152

BCAA, branched-chain amino acids; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; QOL, quality of life.

various intracellular signaling including mammalian target of rapamycin and insulin signaling pathways and exert diverse beneficial effects for cirrhotic patients.[1,2,5,9,53,87,88]

As shown in Table 3, many studies indicated that BCAAs demonstrate favorable effects for albumin synthesis, hepatocarcinogenesis, glucose intolerance/insulin resistance, immunity, and liver regeneration. Early evidence also suggests that BCAAs suppress angiogenesis, hepatic fibrosis, oxidative stress, and hepatitis C virus replication. Thus, we hypothesize that BCAAs may prolong the overall survival of cirrhotic patients. Marchesini et al and Muto et al demonstrated that BCAAs prevented progressive hepatic failure and improved event-free survival in cirrhotic patients, respectively.[3,4] Moreover, a Japanese nationwide study recently revealed that BCAAs prolonged survival of cirrhotic patients by suppressing the onset of life-threatening events.[89] The study also disclosed that in addition to serum alpha-fetoprotein levels and amino acid imbalance, BCAA administration is identified as an independent negative risk factor for life-threatening events in cirrhotic patients.[89]

Conclusion

In this review, we summarized the clinical impacts of BCAA supplementation on HE/MHE and discussed possible mechanisms for BCAA-induced improvement of HE/MHE. The mainstay therapy for HE and MHE is lactulose and antibiotics. BCAAs are expensive and the clinical significance was limited because of small numbers of patients. Thus, BCAA may be an adjunct or alternative to the mainstay therapy for HE and MHE. However, BCAAs serve other beneficial effects on albumin synthesis and development of hepatocellular carcinoma in cirrhotic patients. BCAAs also have potential to improve hepatic fibrosis, insulin resistance, immunity, and patients' quality of life, suggesting that BCAAs seem to have good influence on the management of cirrhotic patients.

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