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Review

Branched-chain amino acid supplementation in treatment of liver cirrhosis: Updated views on how to attenuate their harmful effects on cataplerosis and ammonia formation

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ABSTRACT

Branched-chain amino acid (BCAA; valine, leucine, and isoleucine) supplementation is common for patients with liver cirrhosis due to decreased levels of BCAA in the blood plasma of these patients, which plays a role in pathogenesis of hepatic encephalopathy and cachexia. The unique pharmacologic properties of BCAA also are a factor for use as supplementation in this population. In the present article, BCAA is shown to provide nitrogen to alpha-ketoglutarate (α-KG) for synthesis of glutamate, which is a substrate for ammonia detoxification to glutamine (GLN) in the brain and muscles. The article also demonstrates that the favorable effects of BCAA supplementation might be associated with three adverse effects: draining of α-KG from tricarboxylic acid cycle (cataplerosis), increased GLN content and altered glutamatergic neurotransmission in the brain, and activated GLN catabolism to ammonia in the gut and kidneys. Cataplerosis of α-KG can be attenuated by dimethyl-α-ketoglutarate, L-ornithine-L-aspartate, and ornithine salt of α-KG. The pros and cons of GLN elimination from the body using phenylbutyrate (phenylacetate), which may impair liver regeneration and decrease BCAA levels, should be examined. The therapeutic potential of BCAA might be enhanced also by optimizing its supplementation protocol. It is concluded that the search for strategies attenuating adverse and increasing positive effects of the BCAA is needed to include the BCAA among standard medications for patients with cirrhosis of the liver.

Introduction

A hallmark of cirrhosis of the liver is a decrease in branched-chain amino acids (BCAA; valine, leucine, and isoleucine) in blood plasma caused by enhanced consumption of BCAA in ammonia detoxification to glutamine (GLN) in skeletal muscle [1–4]. Decreased BCAA levels also could be caused by activation of the branched-chain α-ketoacid dehydrogenase by cytokines and cortisol [5,6] and by impaired reamination of branched-chain keto acids (BCKA) by the cirrhotic liver, which is activated in other catabolic conditions [7,8]. A decrease in BCAA is not observed in acute liver damage due to a leak of amino acids from the hepatocytes into circulation [9].

Decreased BCAA levels and the hypothesis that correction of the decreased ratio of BCAA to aromatic amino acids (AAA; tyrosine and phenylalanine) may improve symptoms of hepatic encephalopathy (HE) were the main stimuli for investigations of the therapeutic use of BCAA in patients with liver cirrhosis [10]. Potential benefits of BCAA administration include also their positive effects on protein balance, liver regeneration, albumin synthesis, physical and mental fatigue, and immune function [11,12].

Unfortunately, although there is a good theoretical rationale to administer the BCAA to patients with liver disease, to our knowledge, the results of clinical trials do not provide strong evidence of their therapeutic effectiveness. There are two Cochrane reviews evaluating the results of trials assessing the effects of BCAA supplementation in patients with HE. The authors of the analysis, which was published in 2003, conclude that there is no convincing evidence of the beneficial effects of BCAA on patients with HE [13]. Conclusions of a recent review

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determined that BCAA had a beneficial effect on HE, but no effect on mortality, quality of life, or nutritional parameters [14].

In recent articles [15,16], the relationship between BCAA and ammonia metabolism in liver disease have been explained and some strategies to enhance their therapeutic properties suggested. The present review explored why the results of clinical trials indicate poor evidence of the benefits of BCAA supplementation and provided updated views on how to enhance their therapeutic effectiveness in liver cirrhosis.

Effects of BCAA on ammonia levels in the blood

It is scientific consensus that ammonia plays the main role in pathogenesis of HE, thus most strategies for treatment of HE are targeted at decreasing ammonia. A Medline search found only 14 studies [17–30] of the effects of BCAA on ammonia and their reports are contradictory. Five studies indicated that administration of BCAA has no effect or decreases ammonia (Table 1 [17–21]) and nine studies indicate its increase (Table 2 [22–30]).

Of special interest are observations of enhanced blood ammonia levels after BCAA administration in healthy people during exercise, which is investigated as a potential strategy for treatment of liver disease [31–34]. Because BCAA oxidation in skeletal muscle increases both during exercise and in the presence of liver cirrhosis [35,36], the influence of a combination of BCAA administration and exercise on ammonia levels in patients with liver disease is worth investigation.

In this context, it should be noted that ammonia production during intense exercise is caused primarily by the breakdown of adenine nucleotides to inosine monophosphatate in the adenosine monophosphate deaminase reaction (not by impaired ammonia detoxification to urea as occurs in liver disease) and that moderate exercise at intensities up to 50% maximal oxygen consumption (VO_2 max) has no effect on circulating ammonia [37,38]. A recent study suggests that moderate exercise at an anaerobic threshold (corresponding to 40–60% VO_2 max) combined with 12 g/d BCAA administration improves glycemic control without significant increase in blood ammonia levels in women with liver cirrhosis [34].

The reason for different results in studies reporting the effects of the BCAA on ammonia in patients with liver disease is unknown. The basis for explanation may be an ambivalent effect of BCAA administration on ammonia metabolism in muscle (enhanced ammonia detoxification to GLN) and in the kidneys and enterocytes (increased GLN catabolism to ammonia) as discussed later.

Table 1
Studies reporting unaffected or decreased levels of ammonia after BCAA administration

Study design	Effect of BCAA	Reference
Patients with cirrhosis, 20 g of BCAA or protein added weekly for 4 wk	No effect on ammonia compared with protein groups	[17]
Patients with cirrhosis; BCAA orally (0.24 g/kg) for 3 mo	↓ of ammonia in blood compared with control group	[18]
Patients with cirrhosis; infusion of BCAA-enriched solution	↓ of ammonia during infusion when compared with standard amino acid solution	[19]
Patients with cirrhosis; snack containing 50 g of BCAA at 10:00 p.m. for 2 wk	↓ of ammonia in blood compared with control group	[20]
Rats with portacaval shunt; ammonia and BCAA infusion for 12 h	↓ of ammonia in blood during infusion compared with ammonia salts infusion	[21]

BCAA, branched-chain amino acid

Table 2
Studies reporting increased levels of ammonia after BCAA administration

Study design	Effect of BCAA	Reference
Patients with cirrhosis; BCAA supplemented diet for 2 wk	↑ (transient) ammonia in blood, improvement of HE after 2 wk	[22]
Healthy patients and patients with hepatic failure; BCAA infusion	↑ ammonia (more in hepatic failure)	[23]
Patients with cirrhosis or healthy individuals; BCAA orally (0.45 g/kg)	↑ ammonia and ↑ GLN release from muscle in both groups	[24]
Cycling to exhaustion; 12 g BCAA orally before exercise	↑ ammonia during exercise compared with placebo	[25]
Swimmers, exercise test (60 min swim); BCAA orally (0.2 g/kg) for 1 mo	↑ ammonia during test compared with placebo	[26]
Cycling 100 km; BCAA orally during trial	↑ ammonia in blood during exercise; no difference in performance times	[27]
Men, exercise the knee extensor muscles for 60 min; BCAA orally	↑ ammonia production in muscle	[28]
Rats, swimming exhaustion test; BCAA supplementation for 6 wk	↑ ammonia in blood; negative effect on performance	[29]
Dogs with portocaval shunts and 40% hepatectomy; BCAA-enriched diet	↑ ammonia in blood compared with dogs fed low BCAA diet	[30]

BCAA, branched-chain amino acids; GLN, glutamine; HE, hepatic encephalopathy

BCAA may decrease ammonia levels by enhanced ammonia detoxification to GLN and deplete α-KG from TCA cycle

It has been shown that BCAA acts as a source of nitrogen for synthesis of glutamate, a substrate for ammonia detoxification to GLN, and that hyperammonemia enhances GLN synthesis and BCAA catabolism, resulting in the BCAA deficiency [3,4,39]. Other studies have demonstrated that enhanced BCAA availability activates the rate of BCAA transamination and production of glutamate and GLN in muscles and brain [40,41]. Therefore, the administration of BCAA may decrease ammonia levels by enhanced flux through BCAA aminotransferase leading to increased production of glutamate and ammonia detoxification to GLN (Fig. 1).

Wagenmakers et al. [42] suggested that excessive acceleration of the BCAA catabolism by activated ammonia detoxification to GLN drains alpha-ketoglutarate (α-KG) from tricarboxylic acid (TCA) cycle (cataplerosis) and thus impedes aerobic oxidation (Fig. 1). Another detrimental effect of enhanced ammonia detoxification to GLN, particularly in acute hepatocellular damage, may be the enormous production of GLN in the brain leading to astrocyte swelling, intracranial hypertension, and altered neurotransmission [43]. These suggestions are supported by the decrease of α-KG and other TCA cycle intermediates in skeletal muscle during hyperammonemia, subnormal levels of α-KG in patients with urea cycle disorders, and increased GLN content in slices of brain cortex of rats after addition of the BCAA to incubation medium [40,44,45].

Taken together, it may be hypothesized that enhanced availability of the BCAA promotes adverse effects of activated detoxification of ammonia to GLN, notably in the brain and