Review

Three targets of branched-chain amino acid supplementation in the treatment of liver disease

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Abstract

The article explains the pathogenesis of disturbances in branched-chain amino acid (BCAA; valine, leucine, and isoleucine) and protein metabolism in various forms of hepatic injury and it is suggested that the main cause of decrease in plasma BCAA concentration in liver cirrhosis is hyperammonemia. Three possible targets of BCAA supplementation in hepatic disease are suggested: (1) hepatic encephalopathy, (2) liver regeneration, and (3) hepatic cachexia. The BCAA may ameliorate hepatic encephalopathy by promoting ammonia detoxification, correction of the plasma amino acid imbalance, and by reduced brain influx of aromatic amino acids. The influence of BCAA supplementation on hepatic encephalopathy could be more effective in chronic hepatic injury with hyperammonemia and low concentrations of BCAA in blood than in acute hepatic illness, where hyperaminoacidemia frequently develops. The favorable effect of BCAA on liver regeneration and nutritional state of the body is related to their stimulatory effect on protein synthesis, secretion of hepatocyte growth factor, glutamine production and inhibitory effect on proteolysis. Presumably the beneficial effect of BCAA on hepatic cachexia is significant in compensated liver disease with decreased plasma BCAA concentrations, whereas it is less pronounced in hepatic diseases with inflammatory complications and enhanced protein turnover. It is concluded that specific benefits associated with BCAA supplementation depend significantly on the type of liver disease and on the presence of inflammatory reaction. An important task for clinical research is to identify groups of patients for whom BCAA treatment can significantly improve the health-related quality of life and the prognosis of hepatic disease. © 2010 Elsevier Inc. All rights reserved.

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Introduction

The branched-chain amino acids (BCAAs) valine, leucine, and isoleucine are indispensable amino acids of special interest. The BCAAs serve not only as an essential substrate in the synthesis of body proteins, but also as an important regulator of protein turnover. Several studies have demonstrated the stimulatory effect of BCAAs or their metabolites on protein synthesis and/or inhibitory effect on proteolysis [1–3].

The initial step of BCAA catabolism (Fig. 1), which occurs mostly in skeletal muscles, involves the transfer of the amino group by BCAA aminotransferase (BCAAT) with α-ketoglutarate to form glutamate and branched-chain keto acids (BCKAs). Glutamate is the immediate precursor for synthesis of glutamine released in large amounts by skeletal muscle. In the presence of pyruvate and alanine aminotransferase, glutamate can readily pass BCAA amino groups on to form alanine. Because these reactions are near equilibrium, any large increase in the concentration of substrates for these reactions should result in a subsequent increase in the concentrations of products.

It should be noted that the amino group of the BCAAs could be converted in the skeletal muscle to ammonia and appear as amide nitrogen of glutamine [4]. This could occur by coupling of BCAAT and glutamate dehydrogenase reaction to form a trans-deamination reaction or by the transfer of the amino group of glutamate to oxaloacetate to form aspartate, which is used in the purine cycle for regeneration of adenosine monophosphate. Ammonia is produced by the net
breakdown of adenine nucleotides to inosine monophosphate (IMP) in the adenosine monophosphate deaminase reaction [5].

The BCKAs formed in BCAAT reaction then undergo oxidative decarboxylation, catalyzed by BCKA dehydrogenase (BCKAD), to form the corresponding branched-chain acyl-CoA esters. The BCKAD is a multi-enzyme complex located on the inner surface of the inner mitochondrial membrane that is, unlike that of BCAAT, highly regulated by the phosphorylation–dephosphorylation mechanism. The BCKAD kinase is considered the key regulator of BCKAD activity [6]. It is allosterically inhibited by the BCKA, particularly by α-ketoisocaproate [7]. This may serve as a mechanism promoting the oxidation of excessive quantities of the BCAAs and preventing their catabolism and conservation of BCAAs for protein synthesis in their low concentrations. The BCKAD reaction is irreversible and therefore commits the BCAA to degradation [8]. Hence, the entry of the BCAAs into the catabolic pathway will be dependent on the rate of mitochondrial oxidation of the BCKAs. Beyond the BCKAD reaction, the pathways of the BCAAs diverge into separate steps that eventually lead into the citric acid cycle.

The unique metabolic properties of BCAAs and observations of their enhanced oxidation in sepsis, cancer, trauma, and burns [9–11] led to the investigation of these nutrients in the treatment of patients with proteocatabolic illness. Unfortunately, the resulting studies did not reveal a clear clinical benefit of BCAA supplementation in most disease states [12–15]. However, the positive results of several randomized trials from recent years have indicated their favorable effect in different forms of liver disease [16–20].

Three main targets of BCAA supplementation in the treatment of liver disease can be suggested: 1) prevention and treatment of hepatic encephalopathy, 2) repair and regeneration of hepatic tissue, and 3) prevention and treatment of hepatic cachexia. In all three respects a tremendous number of studies have been performed with the same purpose—to improve quality of life and to promote the survival of patients with hepatic illness (Fig. 2).

Liver disease and amino acids in the blood

Alterations in aminoacidemia in liver disease are determined by a number of factors, such as nutritional status, age, concomitant illness, variceal bleeding, and the type and/or phase of injury development. Clinically important seem to be the differences between the acute and chronic types of hepatic injury and the effect of portal-systemic shunting, the main pathogenic factor of hyperammonemia development in liver cirrhosis.

Acute liver injury

Acute liver injury is a clinical condition resulting from damage of liver cells. Acute liver injury is relatively common due to viruses, drugs (e.g., acetaminophen), or excessive alcohol intake, and in most patients the liver continues to perform vital functions satisfactorily. In approximately 1% of hospitalized cases a very severe clinical condition with a high mortality rate develops, diagnosed usually as acute liver failure and characterized by coagulopathy and encephalopathy [21].

One characteristic feature of acute liver failure is a marked increase in aminoacidemia [22–26]. Because only a moderate increase in plasma amino acid levels may be observed after two-thirds heptectomy [25], the main cause of increased amino acid concentrations in acute liver failure is undoubtedly due to their leaking from the dying hepatocytes into the circulation. Elevation of amino acid concentrations correlates with the extent of hepatic necrosis and thus may have a prognostic significance [26]. The highest increase can be
observed in amino acids with high intracellular concentrations (glutamine, glutamate, alanine, glycine, lysine, threonine, and histidine) and/or in amino acids metabolized predominantly in the liver (phenylalanine, tyrosine, and methionine). The changes in BCAA concentrations are less pronounced because, compared with other amino acids, the BCAs are catabolized significantly in extrahepatic tissues. Therefore, increased [23,24,26,27], unaltered [27], and decreased [22,26] plasma concentrations of BCAs can be observed in acute liver injury.

Chronic injury

Decreased blood concentrations of BCAs and increased concentrations of aromatic amino acids (AAAs) phenylalanine, tyrosine and tryptophan, and methionine are characteristic of chronic hepatic disease, particularly cirrhosis [25,28,29]. The AAAs increase due to a decreased ability to metabolize these amino acids in a diseased liver. Similarly, the cause of increased methionine concentration is its impaired conversion to S-adenosylmethionine. Therefore, the increase in methionine concentration is frequently associated with decreased levels of its metabolites, such as cysteine and taurine, and impaired synthesis of glutathione. The abnormalities in BCAs and AAA levels in cirrhosis are frequently expressed as a molar ratio (valine + isoleucine + leucine)/(phenylalanine + tyrosine). Physiologically, the ratio is 3.0–3.5, whereas in patients with hepatic cirrhosis it is significantly lower.

The pathogenesis of decreased plasma BCAA levels in liver cirrhosis has not been clear for many years, and various metabolic abnormalities have been proposed as the cause, including hyperinsulinemia, hyperglucagonemia, catecholamines, hyperammonemia, and starvation [30–34]. Now it seems to be clear that ammonia has the crucial role [35]. Hyperammonemia develops typically in cases of portal-systemic shunting, when ammonia generated mostly by bacterial degradation of urea and breakdown of glutamine in the gut escapes detoxification by the liver. In this situation, the muscles take up ammonia from the circulation and detoxify it by the synthesis of glutamine from glutamate. Glutamate deficiency intensifies catabolism of BCAs associated with enhanced synthesis of glutamate from a-ketoglutarate. These metabolic alterations are responsible for increased glutamine and decreased BCAA and alanine levels in the blood and skeletal muscle after ammonium salt infusion [36]. An inverse alteration in the concentrations of glutamine (increase) and alanine (decrease) indicates an increased demand for glutamate and decreased alanine synthesis from pyruvate (Fig. 3).

BCAA and hepatic encephalopathy

Hepatic encephalopathy is a serious neuropsychiatric abnormality associated with chronic or acute liver injury. Signs can be impaired cognition, a flapping tremor, and a decreased level of consciousness, including coma, cerebral edema, and ultimately death. In its pathogenesis, changes induced by impaired liver function and portal-systemic shunting interact, resulting in accumulation of substances that are normally removed by the liver. Substances contributing to symptoms of hepatic encephalopathy include mercaptans, short-chain fatty acids, increased concentrations of AAAs, y-aminobutyric acid, “endogenous” benzodiazepines, etc. However, the strongest arguments can be advanced for ammonia, although the exact mechanism by which ammonia causes hepatic encephalopathy is unknown and direct and indirect effects should be considered.

Presumed mechanisms of the direct effect of hyperammonemia on brain functions include its effect on inhibitory postsynaptic potentials by blocking the chloride pump, impairment of brain adenosine triphosphate synthesis due to depletion of Krebs cycle intermediates, cell swelling by ammonia-induced increased cerebral blood flow and synthesis, and accumulation of glutamine in astrocytes [37–41]. Recent studies have demonstrated that hyperammonemia significantly affects neurotransmission associated with n-methyl-D-aspartic acid–type glutamate receptors [42]. The effect seems to be different in acute and chronic hepatic diseases. Acute ammonia intoxication leads to the activation of n-methyl-D-aspartic acid receptors and to the entry of Ca2+ from the extracellular space to the postsynaptic neuron. The intracellular excess of Ca2+ is associated with increased formation of nitric oxide, increased production of free radicals, impaired mitochondrial respiration, and adenosine triphosphate depletion, which may contribute to the ammonia-induced death in acute liver failure [43]. Chronic hyperammonemia seems to induce impaired signal transduction.
associated with n-methyl-D-aspartic acid receptors, possibly contributing to some neurologic alterations observed in hepatic encephalopathy [44].

Indirectly, hyperammonemia may contribute to hepatic encephalopathy by a decrease in BCAA levels in the blood and by alterations in amino acid transport across the blood–brain barrier, as Fischer and Baldessarini [45] suggested in their “false neurotransmitter” hypothesis. The AAAs flood the central nervous system due to high blood plasma concentrations of AAA and low concentration of BCAAs, which compete for entry by the L-system (system that serves for transport of neutral amino acids) across the blood–brain barrier. Augmented uptake of AAAs could result in an imbalance in the synthesis of dopamine, noradrenaline, and serotonin in the brain. In addition, increased availability of AAAs may cause the formation of “false neurotransmitters” such as octopamine, phenylethanolamine, and tyramine.

The rationale of BCAs in the treatment of hepatic encephalopathy was based on assumptions that providing BCAs would facilitate ammonia detoxification by supporting glutamine synthesis in skeletal muscle and in the brain, normalize plasma amino acid concentrations, and decrease brain influx of AAAs. Many clinical studies have confirmed abnormalities in amino acid concentrations in liver cirrhosis and demonstrated the favorable effect of BCAs on hepatic encephalopathy [46–52]. However, despite strong theoretical presumptions and promising results of many clinical studies mentioned earlier, the randomized trials failed to confirm the efficacy of BCAs in treatment of hepatic encephalopathy [53–55]. It is beyond the scope of this review to discuss in detail the studies investigating the ability of BCAs to ameliorate hepatic encephalopathy. The reader is referred to the review by Als-Nielsen et al. [55] in which problems with the methodologic quality of some trials are noted, e.g., the number and compliance of patients, patients’ heterogeneity, and interpretation of obtained results.

Treatment with BCAs is assumed to be more effective in chronic hepatic injury with hyperammonemia and low BCAA/AAA ratios, whereas in acute injury or in case of exacerbation of chronic hepatic illness, when hyperammonoacidemia and hyperosmolarity develop, BCAA administration can be detrimental. Furthermore, some studies have shown that, when circulating BCAA levels are non-physiologically elevated by supplementation, a significantly greater production of ammonia occurs in skeletal muscle [56]. Therefore, an important task for clinical research seems to be performing well-conducted long-term trials that would evaluate not only the effect of BCAs on hepatic encephalopathy development but also the effect of BCAA supplementation on ammonia and amino acid concentrations in body fluids.

**BCAA and liver regeneration**

The survival of patients with liver injury of varying etiologies depends on the ability of the remaining hepatocytes to regenerate. The knowledge of how to stimulate liver regeneration can increase the survival rate of patients with acute liver failure and decrease the recovery period after liver resection or transplantation.

Nutritional and/or metabolic support of liver regeneration seem to be very important, particularly in the case of major liver resection, which has become the gold standard of treatment for a wide range of primary and secondary liver malignancies. As a principal source of energy for these patients, carbohydrates, primarily glucose, are recommended. The main rationale is the risk of hypoglycemia development. Results of several studies have indicated that preservation of hepatic glycogen increases the liver’s tolerance to oxidative and ischemic damage [57,58] and that a perioperative glucose/insulin infusion may prevent or attenuate hepatic dysfunction after extensive liver resection [59].

However, the results of many experimental studies have suggested that the regenerating liver generates adenosine triphosphate primarily by oxidation of fatty acids, and that glucose administration inhibits, whereas infusion of fatty emulsion stimulates, liver regeneration [60–62]. The inhibitory effect of glucose on liver regeneration can be explained by decreased mobilization of fatty acids as a result of inhibition of hormone-sensitive lipase by insulin [60] and by an increase in the insulin/gluconeon quotient, a change known to inhibit liver regeneration [63]. The extensive fatty acid oxidation in a regenerating liver can explain the beneficial effect of carnitine (the essential cofactor in the transfer of fatty acids across the inner mitochondrial membrane) on liver regeneration [64]. Fatty acids also act as a substrate for synthesis of phospholipids and for esterification of cholesterol, important components of newly synthesized cell membranes. The positive effect of exogenous phospholipids on liver regeneration has been demonstrated in animal studies [65] and may explain the therapeutic effect of polyunsaturated phosphatidylcholine in hepatic damage therapy [66]. Many studies have demonstrated that lipids are well tolerated, even in cirrhotic patients, if administered parenterally [67,68]. Clinical trials will have to determine whether lipid therapy can improve liver regeneration and function after liver resection and in hepatic disease.

The demands of regenerating hepatic tissue for a supply of amino acids are undoubtedly higher than in a physiologic state. Nevertheless, it seems that it is not necessary to increase the intake of some amino acids with the intent to stimulate liver regeneration or the required amounts can perhaps even be lower. Such amino acids include AAAs, the levels of which are usually increased in hepatic injury, whereas a decreased concentration of some amino acids, particularly taurine, threonine, and BCAA, below control values in the phase of liver recovery indicates increased utilization of these amino acids and the importance of their endogenous supply [26].

The beneficial effect of BCAA administration on liver regeneration has been demonstrated in a number of experimental studies [69–71]. Unfortunately, it is not easy to study the process of liver repair and regeneration in clinical
practice, and the available data are mostly based on tests of liver function. As an example, BCAA treatment promoted recovery of serum albumin and lowered bilirubin levels after partial hepatectomy for liver cancer [72,73] and improved patients’ prognosis after liver transplantation [74].

The mechanism of the favorable effect of BCAAs on hepatic tissue repair is undoubtedly multifactorial. In addition to the increased requirements of the regenerating liver, the well-known synergistic effect of glucagon and insulin on liver regeneration [75], the stimulatory effect of leucine on protein synthesis [1,3], and/or the stimulatory effect of leucine on secretion of hepatocyte growth factor by hepatic stellate cells [76] may be involved. Some effects of BCAAs may be associated also with enhanced production of glutamine, which proved to have a significant stimulatory effect on liver regeneration after partial hepatectomy [77,78]. However, considering that severe disturbances in ammonia metabolism in liver cirrhosis are associated with increased glutamine concentrations, the suggestion to enhance the delivery of glutamine in patients with liver disease seems problematic.

**BCAA and hepatic cachexia**

Cachexia is defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass [79]. The reports of the prevalence of hepatic cachexia are not consistent, and vary from 20% in patients with compensated liver disease to 100% in patients with acute alcoholic hepatitis [80,81]. The prevalence of cachexia in patients with liver cirrhosis is about 50% [82].

The pathogenesis of hepatic cachexia is not fully understood. Poor dietary intake, malabsorption, maldigestion, and metabolic disturbances, resulting in changes in protein synthesis and proteolysis, are undoubtedly involved. Most patients with chronic liver disease are characterized by impaired glucose tolerance and diabetes mellitus develops in some of them [83]. Impaired postprandial glucose utilization contributes to decreased glycogen contents in the liver and skeletal muscle, a disturbed supply of glucose from the liver during fasting, enhanced utilization of lipids and proteins for energy, and consequently to development of a catabolic state. In liver cirrhosis the important energy substrate for skeletal muscle are BCAAs taken up from plasma and muscle proteins and then catabolized. In the first step of their catabolism they are used for glutamate synthesis in mitochondria to clear blood ammonia by enhanced production of glutamine (Fig. 3). In the second step, most BCKAs produced in BCAAT reaction are oxidized, probably mostly in the skeletal muscle [84,85].

Measurements of protein and/or BCAA turnover in subjects with cirrhosis are not consistent with increased [86–88], unchanged [89–91], and decreased [85,92] turnover rates being reported. It seems that two metabolically different situations can develop in liver cirrhosis (Fig. 4).

In well-compensated cirrhosis, muscle wasting is probably due more to decreased protein synthesis than to increased protein catabolism [82,92]. Presumably the main changes in protein turnover in skeletal muscles of cirrhotic subjects are caused by hyperammonemia and associated with preferred oxidation of BCAAs. Several studies have indicated a strong inhibitory effect of ammonia on protein synthesis [93] and its lysosomotropic toxicity [94,95]. This suggestion may be supported by observing decreased resting energy expenditure in cirrhotic patients treated by transjugular intrahepatic porto-systemic stent-shunt to decrease portal hypertension [96]. Decreased protein turnover may be also secondarily due to decreased intake of food, maldigestion, and malabsorption [97] and/or to decreased concentrations of BCAAs and increased concentrations of glutamine caused by hyperammonemia [98,99].

The contributing complications and infections that are often undiagnosed in patients with cirrhosis may induce a systemic response associated with an enhanced production of cytokines, sympathetic nervous system activation, enhanced cortisol production, etc., followed by a complex of metabolic alterations in the body, particularly by activated proteolysis in skeletal muscle and enhanced BCAA oxidation [9–11]. Because of the enhanced release of BCAAs from muscle proteins, the BCAA deficiency in body fluids may not be observed and/or may disappear. These patients tend to be hypermetabolic and a higher supply of dietary protein may be required to achieve a positive nitrogen balance. These suggestions are supported by the study of Thomsen et al. [100] who showed that endotoxin administered to cirrhotic rats induced changes in the insulin-like growth factor system that facilitates catabolism.

**Fig. 4.** Protein metabolism in stable cirrhosis and in cirrhosis complicated by SIR. 1) Characteristic metabolic response in stable cirrhosis seems to be decreased protein turnover, probably due to increased concentrations of ammonia and glutamine, decreased concentrations of BCAAs, and decreased food intake. Thus the cause of muscle wasting is the greater decrease in PS than in PL. 2) A characteristic response in cirrhosis associated with SIR is enhanced protein turnover, mainly because of action of cytokines released during activation of the immune system. The cause of muscle wasting may be a greater increase in PL than in PS. BCAA, branched-chain amino acid; PL, protein synthesis; PS, systemic inflammatory reaction.
Several studies have demonstrated that administration of amino acid formulas enriched with BCAAs can reduce protein loss, support protein synthesis, and improve the nutritional status of patients with hepatic illness [17,20,101]. This favorable effect of BCAAs on liver disease development makes liver illness exceptional, particularly in comparison with other proteocatabolic disorders, such as sepsis, burn injury, and cancer, in which positive therapeutic effects of BCAA supplementation are not convincing [15]. One possible explanation may be based on the existence of decreased BCAA levels in liver cirrhosis, which indicates a deficiency of these indispensable amino acids and a clear rationale for BCAA supplementation. However, the decrease in plasma BCAAs is not a constant finding in hepatic illness, particularly in hepatic disease exacerbation and if inflammatory complications develop. In addition, it seems that the inflammatory response blunts the anabolic response after BCAA administration. Lang and Frost [102] demonstrated that leucine-induced activation of eukaryotic initiation factor eIF4E is abrogated in endotoxin-treated rats and that endotoxin treatment antagonizes the leucine-induced phosphorylation of ribosomal protein S6 and mammalian target of rapamycin (mTOR). Therefore, one can assume that BCAA supplementation is more effective in compensated cirrhosis with decreased plasma BCAA concentrations and without symptoms of an inflammatory response of the body. Unfortunately, there are no clinical studies investigating this important topic in practice. In such studies, which should be carried out for at least several months, the nutritional and immune statuses of patients should be carefully evaluated before BCAA supplementation to confirm the presence of cachexia and signs of inflammation. The assessment of changes in body weight, appetite, muscle strength, fat-free mass index, inflammatory markers (C-reactive protein and interleukin-6), albumin, ammonia, and amino acid concentrations in the blood seems to be particularly important.

The mechanism of the favorable effect of BCAAs on protein metabolism and nutritional state of patients with hepatic disease is undoubtedly related to their well-known stimulatory effect on protein synthesis and inhibitory effect on proteolysis [1]. Leucine stimulates insulin release from β-cells of the pancreas [103] and there are emerging data that BCAAs, particularly leucine, stimulate protein synthesis through the mTOR signaling pathway and phosphorylation of translation initiation factors and ribosomal proteins [3]. These effects may contribute to the improvement of insulin resistance and β-cell function in patients with chronic liver disease after BCAA treatment [104]. The inhibitory effect of BCAAs on proteolysis is probably mediated by several metabolites of BCAAs, particularly of the BCKAs and β-hydroxy-β-methylbutyrate [1,105,106].

Conclusions and suggestions for further studies

Most experimental and clinical studies comparing the effect of BCAA supplementation with any kind of control therapy in chronic hepatic disease have revealed the favorable effect of BCAAs on nutritional status, development of liver illness, and quality of life. The mechanism of this favorable effect is probably related to the unique metabolic properties of BCAAs, particularly those of leucine, which include its stimulatory effect on protein synthesis, insulin secretion, and liver regeneration. These favorable effects of BCAA supplementation seem to be more apparent when BCAA concentrations decrease, which is characteristic for liver cirrhosis, particularly with portal-systemic shunts, and when liver disease is not complicated by a systemic inflammatory response. Unfortunately, the results of clinical studies evaluating the effect of BCAA on development of hepatic encephalopathy are not convincing. Further randomized clinical trials involving more patients with a specified type of chronic hepatic illness (preferably with hyperammonemia and decreased BCAA/AAA ratio) carried out for at least several months are desirable to answer the nearly 40-y-old question of BCAA effectiveness in treating hepatic encephalopathy.

Formulas for oral, enteral, and parenteral BCAA supplementation are commercially available and the appropriate administration route should be considered. There is no evidence of differences in therapeutic effects of BCAAs when administered by the parenteral or enteral route [55,107]. One possible advantage of the oral route may be a better hepatic supply of the BCAAs, namely of leucine, which is a potent agent activating the protein synthesis [1,3] and hepatocyte growth factor expression [76]. Because long-term intervention is an important issue in management of liver disease and parenteral feeding can be deleterious for a patient (e.g., danger of liver steatosis, impaired gut hormonal and immunologic responses, and phlebitis or thrombosis of the veins), the oral route should be preferred. An adverse property of BCAAs is their extremely bitter taste, and the low palatability of nutritive drinks is a major problem with respect to patient compliance [108]. The suppression of the bitterness and improvement of the palatability of products containing BCAAs may significantly contribute to the therapeutic effect of these supplements.

The BCAA-enriched mixtures should contain not only BCAAs but also glucose, lipids, and other nutrients that should have beneficial effects on the course of hepatic illness. The simultaneous administration of BCAAs with glucose seems to be particularly important. In several studies it was demonstrated that BCAA improves insulin resistance and thus BCAA-enriched supplements may be a useful therapeutic approach for improving glucose utilization. This favorable effect of BCAAs, especially that of leucine, can be mediated by promoted glucose utilization by phosphoinositide 3-kinase and protein kinase C pathways, by activated glycogen synthase by mTOR signals in the skeletal muscle [16], and by the stimulating effect of leucine on insulin release from β-cells of the pancreas [103]. Coadministration of BCAAs with carnitine and/or with zinc seems also to be promising. Malaguarnera et al. [109] recently demonstrated that administration of BCAA supplemented with l-acetylcarnitine has a more
significant effect on improvement of neurologic symptoms and serum ammonia in cirrhotic patients compared with patients treated only by BCAAs. Simultaneous 6-mo treatment with BCAAs and zinc supplements in patients with liver cirrhosis showed a significantly higher efficacy in correcting amino acid alterations and a greater ability to metabolize ammonia than in patients treated by a BCAA mixture alone [110]. Further investigation is necessary also to determine the effect of BCAA administration and the effectiveness of the most widely used therapies in decreasing the production and absorption of gut-derived neurotoxic substances, especially ammonia. Attention should be paid to disaccharides (lactulose and lactitol) and antimicrobials (rifaximin, metronidazole, and vancomycin).

In conclusion, although critical objections regarding the effects of BCAAs can still be raised, the rationale of BCAA administration in chronic hepatic illness, their favorable effect on nutritional state, repair and regeneration of hepatic tissue, safety of their administration, and positive results of several randomized trials conducted in recent years are strong arguments for BCAA supplementation as a standard nutritional approach in treating patients with hepatic disease, particularly cirrhosis. The crucial problem seems to be the patients’ group determination, in which BCAA treatment can significantly improve the quality of life and prognosis of hepatic disease. It seems that specific benefits associated with BCAA supplementation depend significantly on the type of liver disease and whether an inflammatory and/or a stress reaction are present.

References


