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Review

Branched-chain amino acids and ammonia metabolism in liver disease: Therapeutic implications

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ABSTRACT

The rationale for recommendation of branched-chain amino acids (BCAA; valine, leucine, and isoleucine) in treatment of liver failure is based on their unique pharmacologic properties, stimulatory effect on ammonia detoxification to glutamine (GLN), and decreased concentrations in liver cirrhosis. Multiple lines of evidence have shown that the main cause of the BCAA deficiency in liver cirrhosis is their consumption in skeletal muscle for synthesis of glutamate, which acts as a substrate for ammonia detoxification to GLN and that the BCAA administration to patients with liver failure may exert a number of positive effects that may be more pronounced in patients with marked depression of BCAA levels. On the other hand, due to the stimulatory effect of BCAA on GLN synthesis, BCAA supplementation may lead to enhanced ammonia production from GLN breakdown in the intestine and the kidneys and thus exert harmful effects on the development of hepatic encephalopathy. Therefore, to enhance therapeutic effectiveness of the BCAA in patients with liver injury, their detrimental effect on ammonia production, which is negligible in healthy people and/or patients with other disorders, should be avoided. In treatment of hepatic encephalopathy, simultaneous administration of the BCAA (to correct amino acid imbalance and promote ammonia detoxification to GLN) with α-ketoglutarate (to inhibit GLN breakdown to ammonia in enterocytes) and/or phenylbutyrate (to enhance GLN excretion by the kidneys) is suggested. Attention should be given to the type of liver injury, gastrointestinal bleeding, signs of inflammation, and the dose of BCAA.

Introduction

In recent decades, the role of supplementation of the branched-chain amino acids (BCAA; valine, leucine, and isoleucine) in the treatment of liver disease has been studied extensively both in animal models and in humans. A number of studies have reported their favorable effects on hepatic encephalopathy [1–5], protein balance [6], and liver regeneration [7–9]. Unfortunately, their administration to patients with liver disease has yielded conflicting results and the enthusiasm for BCAA dwindled in 1990s, when large clinical trials failed to confirm their efficacy in the treatment of hepatic encephalopathy [10–12].

Now the interest for BCAA has recovered and some important papers recommending the BCAA appeared recently [13–21], the European Society for Clinical Nutrition and Metabolism guidelines recommend the use of BCAA-enriched supplements in patients with hepatic encephalopathy arising during enteral nutrition [22]. Particularly interesting are the results of a randomized study that included patients with cirrhosis and a previous episode of hepatic encephalopathy in which BCAA did not decrease recurrence of hepatic encephalopathy but improved minimal hepatic encephalopathy [23]. A meta-analysis of randomized controlled trials found that oral BCAA supplements have beneficial effects on manifestations of hepatic encephalopathy compared with control supplements [24]. Unfortunately, the explanation for the lack of success of enhanced intake of BCAA reported in a number of clinical trials is lacking.

The first aim of this contribution is to demonstrate that in patients with liver failure, BCAA administration may, in addition to a number of positive effects, exert an adverse effect on ammonia production due to its role in glutamine (GLN) synthesis, thus impairing its therapeutic effectiveness. The second aim is to suggest how the negative effect of BCAA intake on ammonia production can be avoided.

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Favorable effects of BCAA supplementation in liver disease

The BCAA exert a number of exceptional regulatory functions that may play a role in their beneficial effects in the treatment of liver failure. First, in skeletal muscle the BCAA stimulate synthesis of GLN from glutamate and ammonia [25–27] and thus activate an alternative pathway of ammonia detoxification. The BCAA, especially leucine, improve glucose metabolism by acting both on insulin release from β cells of the pancreas [28] and on insulin target organs such as skeletal muscle, adipose tissue, and the liver [29]. In the liver, they promote protein synthesis via mammalian target of rapamycin (mTOR) signaling pathways and phosphorylation of translation initiation factors and ribosomal proteins [30,31] and stimulate secretion of hepatocyte growth factor by hepatic stellate cells [32]. Moreover, it has been reported that the BCAA prevent accumulation of tissue triglycerides and enhance expression of peroxisome proliferator-activated receptor-α [33]. Also their beneficial effect on function of dendritic cells, phagocytic function of neutrophils, and natural killer activity of lymphocytes seems important [34–36]. Several metabolites of BCAA, particularly branched-chain keto acids and β-hydroxy-β-methylbutyrate, exert inhibitory effect on proteolysis in skeletal muscle [37–39].

BCAA deficiency and therapeutic effectiveness of the BCAA

Considering the exceptional pharmacologic properties of the BCAA just specified, their deficiency should negatively affect the course and outcome of liver disease. The decrease of plasma BCAA levels is a hallmark of liver cirrhosis [40,41] and it might be suggested that the favorable effects of BCAA supplementation on hepatic encephalopathy, protein balance, glucose tolerance, immunity, and liver functions reported in a number of studies result mostly (if not entirely) from corrections of disadvantages resulting from their deficiency. Therefore, theoretically, BCAA supplementation might be of benefit particularly in patients with low BCAA levels.

The pathogenesis of BCAA deficiency in liver cirrhosis was obscure for many years. Now it is clear that the main role is fulfilled by enhanced detoxification of ammonia to GLN where the BCAA act as an essential donor of nitrogen to form glutamate that reacts with ammonia in GLN synthetase reaction (Fig. 1). The role of ammonia detoxification to GLN in development of BCAA deficiency has been demonstrated by enhanced BCAA catabolism and decreased BCAA levels in rats after infusion of ammonium salts [42,43] and by decreased leucine oxidation in skeletal muscle after treatment by GLN synthetase inhibitor [44]. Considering the tissue mass and distribution of BCAA aminotransferase and GLN synthetase activities, the main place of GLN synthesis and BCAA catabolism is skeletal muscle [45]. A clear demonstration that hyperammonemia directly activates GLN synthesis and BCAA catabolism in skeletal muscle and decreases BCAA concentration in extracellular fluid was given recently using isolated skeletal muscle [46].

The decreased levels of circulating BCAA have been, together with increased levels of aromatic amino acids (AAA; phenylalanine, tyrosine, and tryptophan), implicated by Fischer and Baldessarini in their "false neurotransmitter" hypothesis as a possible cause of hepatic encephalopathy (Fig. 2). They postulated that due to the decreased ratio of concentrations of BCAA to AAA, the AAA flood the central nervous system and cause an imbalance in synthesis of dopamine, noradrenaline, and serotonin or may cause formation of false neurotransmitters such as octopamine, phenylethanolamine, and tyramine [47].

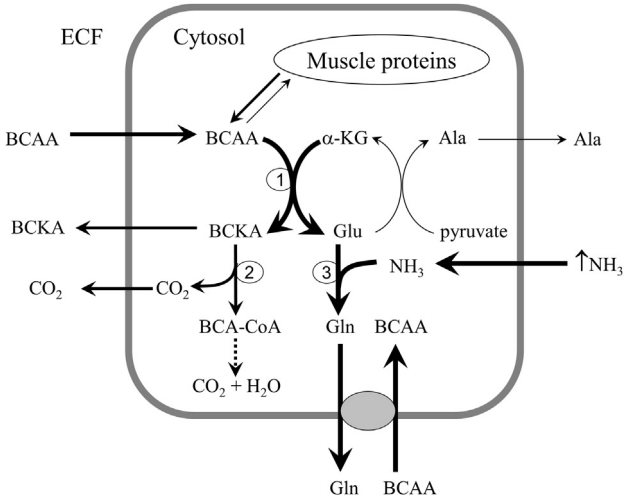

Fig. 1. Effects of hyperammonemia on GLN and BCAA metabolism in skeletal muscle [46]. Hyperammonemia activates GLN synthesis that may enhance consumption of BCAA resulting in their deficiency in extracellular fluid. 1, branched-chain aminotransferase; 2, branched-chain α-ketoacid dehydrogenase; 3, GLN synthetase. BCA-CoA, branched-chain acyl-CoA.

Therefore, the decreased serum ratio of BCAA to AAA may be considered as the rational basis for employment of the BCAA in treatment of hepatic encephalopathy.

In the presence of hyperammonemia, brain uptake of AAA rises also because ammonia stimulates GLN synthesis and exchange of brain GLN for plasma-neutral amino acids [48]. There is strong evidence that GLN accumulation in astrocytes contributes to the development of hepatic encephalopathy [49].

Effects of BCAA supplementation on ammonia production

The initial site of BCAA catabolism after their oral or parenteral administration is considered skeletal muscle because of a high activity of BCAA aminotransferase. Enhanced BCAA availability activates the flux of the BCAA through BCAA aminotransferase reaction and release of GLN and alanine from skeletal muscle [25–27]. Both amino acids are extracted from circulation by the splanchnic bed, especially by enterocytes, and catabolized

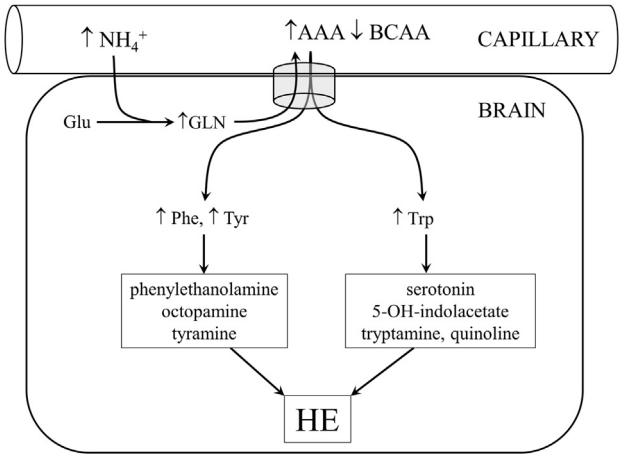

Fig. 2. Alterations in synthesis of neurotransmitters resulting from reduced BCAA/AAA ratio in the blood and enhanced GLN synthesis in the brain. See text for discussion.