Review Article

Branched-chain amino acids in liver diseases

Kazuto Tajiri[1], Yukihiro Shimizu[2]

[1]Department of Gastroenterology, Toyama University Hospital, Toyama, Japan; [2]Gastroenterology Unit, Nanto Municipal Hospital, Nanto, Japan

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Correspondence to: Kazuto Tajiri, MD, PhD. Department of Gastroenterology, Toyama University Hospital, 2630 Sugitani, Toyama 930-0194, Japan. Email: tajikazu@med.u-toyama.ac.jp.

Abstract: Branched chain amino acids (BCAAs) are involved in various bioprocess such as protein metabolism, gene expression, insulin resistance and proliferation of hepatocytes. BCAAs have also been reported to suppress the growth of hepatocellular carcinoma (HCC) cells *in vitro* and to be required for immune cells to perform the function. In advanced cirrhotic patients, it has been clarified that serum concentrations of BCAA are decreased, whereas those of aromatic amino acids (AAAs) are increased. These alterations are thought to be the causes of hepatic encephalopathy (HE), sarcopenia and hepatocarcinogenesis and may be associated with the poor prognosis of patients with these conditions. Administration of BCAA-rich medicines has shown positive results in patients with cirrhosis.

Keywords: Branched chain amino acids (BCAAs); cirrhosis; mammalian target of rapamycin signal (mTOR signal); hepatocarcinogenesis; immunity

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Introduction

The branched chain amino acids (BCAAs), valine (Val), leucine (Leu) and isoleucine (Ile), are essential amino acids for human beings and are involved in the pathophysiology of liver diseases (1). This review describes the biological properties of BCAAs and their clinical use in the management of liver cirrhosis. In addition, this review describes the role of BCAAs to suppress hepatocarcinogenesis and their potential role in the treatment of hepatocellular carcinoma (HCC).

Basic aspects of BCAAs in the liver

BCAAs and metabolism

BCAAs are involved in the metabolism of proteins, glucose and fats. BCAAs activate mammalian target of rapamycin (mTOR) signaling, stimulating the synthesis of glycogen and of proteins such as albumin (1,2). mTOR is involved in the phosphoinositide-3-kinase-protein kinase B (PI3K-Akt) signaling pathway (3) and plays central roles in cell growth (4), proliferation (5) and insulin resistance (6) (*Figure 1*).

Glucose and lipid metabolism

BCAAs regulate the metabolism of glucose and lipids through the PI3K-Akt pathway. Ile was shown to mediate glucose uptake by PI3K independent of mTOR (7) and to decrease the level of plasma glucose (7). BCAAs have been shown to promote the uptake of glucose by skeletal muscle through activation of PI3K and protein kinase C, and subsequently induce glucose transporter translocation to the plasma membrane (8). Deficiencies in BCAAs reduce hepatic fatty acid synthesis, promote fatty acid β-oxidation and increase fat mobilization in white adipose tissue through the AMP-activated protein kinase (AMPK)-mTOR-FoxO1 pathway (9,10). In adipose tissue, Leu increases insulin-induced phosphorylation of mTOR and Akt, and then enhances the uptake of glucose (11). In addition, BCAAs increase peroxisome proliferator-activated receptor (PPAR)-γ and subsequently uncoupling protein

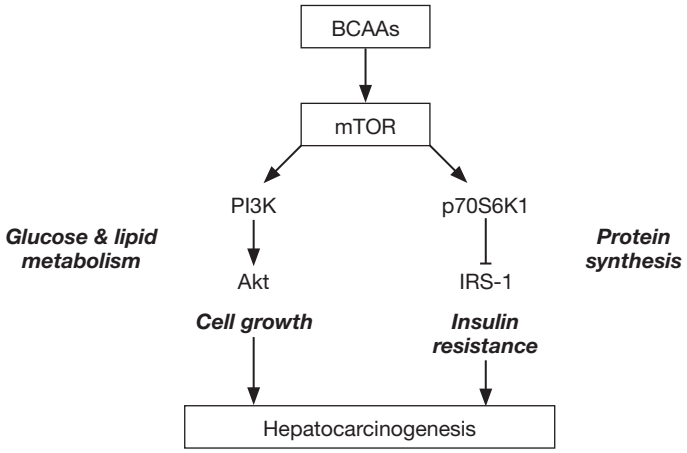

Figure 1 Mechanism of BCAAs-stimulated mTOR signaling and hepatocarcinogenesis. PI3K-Akt, phosohoinositide-3-kinase protein kinase B; p70S6K1, p70 S6 kinase 1; IRS-1, insulin receptor substrate; mTOR, mammalian target of rapamycin; BCAAs, branched-chain amino acids.

2 (UCP2) in liver and UCP3 in muscle through glucose transporter 4 (GLUT4) translocation (12), stimulating oxidation of free fatty acids and reducing triglyceride concentrations in mouse livers (13). Thus, BCAAs regulate fatty acid synthesis, transport, oxidation, lipolysis and adipokine secretion by affecting the expression of genes encoding AMPKα, mTOR, sirtuin-1 (SIRT-1) and PPAR-γ coactivator-1α (PGC-1α) (14). Furthermore Krüppel-like factor 15, a transcription factor, was shown to be involved in regulating the metabolism of glucose, lipids and amino acids (15).

Protein synthesis

BCAAs, especially Leu, contribute to protein synthesis through the mTOR pathway (16). Leu induces the phosphorylation of p70S6 kinase 1 (S6K1) and 4E-binding protein 1 (4EBP1) and the assembly of eukaryotic initiation factor 4E (eIF4E) in mTOR signaling (16), resulting in the synthesis of albumin (17-19). Leu also stimulates albumin mRNA translation through nuclear importation of polypyrimidine-tract-binding protein (20).

BCAA metabolites, such as branched-chain α-keto acids (BCKA), β-hydroxy-β-methyl butyrate (HMB) and glutamate, are also involved in regulating protein synthesis (21). BCKAs were shown to decrease protein expression in cardiomyocytes through mTORC2-Akt signaling (22). HMB was also shown to be involved in muscle protein synthesis and degradation through the mTOR signaling pathway, mainly through mTORC1 (23-25).

Insulin resistance

The activation of mTORC1 promotes insulin resistance through serine phosphorylation of insulin receptor substrate (IRS)-1 and IRS-2 (3). Serum BCAA concentrations were found to be elevated in mice lacking mitochondrial BCAA aminotransferase that catalyzes BCAAs. Those mice show lower fasting blood glucose and insulin concentrations, and homeostasis model assessment scores for insulin resistance (HOMA-IR) were significantly lower as compared with those in wild-type mice (26). Furthermore, administration of Leu or Ile improved insulin sensitivity in mice fed with high-fat diets (27,28). Improvement of insulin resistance by BCAAs has been found to be achieved by several mechanisms (1). For example, BCAAs were found to stimulate liver-type glucokinase and glucose transporter (29), as well as to suppress hepatic expression of glucose-6-phosphatase. BCAAs were also reported to transiently increase plasma concentrations of insulin in healthy individuals (30). BCAAs were found to improve HOMA-IR scores and the function of beta cell in patients with chronic liver disease (31). These results strongly suggest that BCAAs can ameliorate insulin resistance (1).

BCAA and hepatocyte proliferation

BCAA has been associated with cell proliferation through activation of mTORC1 (32). In a rat model of CCl_4-induced liver injury, the supplementation of BCAA was shown to suppress hepatocyte apoptosis leading to retardation of the progression of the injury (33). In contrast, BCAAs enhanced

hepatocyte regeneration in a rat hepatectomy model (34) and were shown to increase the secretion of hepatocyte growth factor (35). BCAAs are also shown to suppress oxidative stress by stimulating the expression of PGC-1α or SIRT-1 (36), or by activating the genes involved in antioxidant defenses (37). Those mechanisms could also contribute to promote hepatocyte proliferation.

BCAA and immunity

Nutrition is shown to be closely associated with the maturation or activation of immunity, and BCAAs are reported to be directly involved in the proliferation of lymphocyte or the maturation of dendritic cells (DCs) (1). All of the three BCAAs are shown to be requisite for mitogen-induced lymphocyte proliferation (38), and Val has the most prominent effect for the proliferation of lymphocytes.

The importance of BCAAs for immunity has been also shown *in/by vivo* studies. We previously evaluated the role of BCAAs on the local immune function in the liver and spleen of rats (36). We found that supplementation of BCAAs increased the numbers of intrahepatic lymphocytes and stimulated natural killer (NK) cells and lectin-dependent cytotoxic activities in the liver. It is of note that the number of lymphocytes isolated form the liver was increased as the concentrations of Val increased in plasma and liver. Importance of valine for the stimulation of immune response is supported by a report by Kakazu *et al.*, in which they report the critical role of Val in the maturation of DCs (37). These findings indicate that Val may have a therapeutic potential for reducing hepatocarcinogenesis in patients with cirrhosis by restoring the immune functions (1,37,39).

In patients with liver cirrhosis, BCAA supplementation has been shown to increase the numbers of intrahepatic lymphocytes and restores the phagocytic activity of neutrophils and NK activity (40,41). Furthermore, the supplementation of BCAAs was shown to increase the number of circulating lymphocytes in postsurgical patients (42,43). BCAA supplementation in patients with chronic hepatitis C can restore malnutrition-association impairments in interferon signaling through the mTOR and FoxO pathways (44). Interestingly, supplementation of Val was shown to reduce hepatitis C viral load, which could be caused by enhancing DC function or interferon signaling (45). BCAAs were also shown to increase immunoglobulin A secretion, which could enhance mucosal surface defenses (46). Thus, BCAAs could regulate both innate and adaptive immune responses.

Serum concentration of BCAAs in cirrhotic patients

In patients with advanced cirrhosis, decreased serum concentrations of BCAA and increased concentrations of aromatic amino acids (AAAs), phenylalanine and tyrosine, are often found, resulting in a decreased ratio of BCAAs to AAAs, called the Fischer ratio (47). A decreased Fischer ratio is thought to be a cause of hepatic encephalopathy (HE) (1). Fischer ratio tends to become lower with the progression of cirrhosis, which could help assess the prognosis of cirrhotic patients with or without HCC (48,49). Moreover, a simplified Fischer ratio, the BCAA to tyrosine ratio (BTR), has been shown to be useful for the prediction of albumin concentration 1 year later (50). BTR was also reported to be useful in predicting the prognosis of patients with liver cirrhosis (51). These data suggest that the imbalance of amino acid, either decreased Fischer ratio or BTR, is an indicator for progression and prognosis of cirrhosis, and that correcting either ratio may be useful not only for nutritional improvement, but also for prevention of HE, in patients with cirrhosis (1).

Clinical application of BCAA supplementation in liver cirrhosis

BCAAs for liver cirrhosis

Since the liver is a central organ for nutrient metabolism, cirrhotic patients may develop various metabolic complications (52). Patients with cirrhosis frequently show protein and energy deficiencies. Protein deficiencies could lead to hypoalbuminemia, resulting in ascites retention and hepatic edema, whereas energy deficiencies could reduce fat and muscle mass and cause muscle weakness, both of which may significantly reduce their quality of life (QOL) (53). Significant improvement of QOL and prognosis in patients with cirrhosis can be achieved by the supplementation of BCAA. Two randomized trials showed a significant improvement of Short Form-36 scores of general health perception by BCAA supplementation (54,55). Another randomized study showed that BCAA supplementation improved weakness and fatigue (56). The supplementation of BCAA was also reported to improve sleep disturbance (57).

A large-scale post marketing study in Japan showed that oral BCAA administration significantly reduced the

incidence of complications such as liver failure, esophageal varices rupture, HCC, and death (55). Furthermore, the supplementation of BCAA in cirrhotic patients showed the improvement of glucose metabolism and an increase in serum albumin concentration (58), and the effect of BCAA on maintenance or an increase in serum albumin concentrations in patients with both compensated and decompensated cirrhosis was confirmed by a randomized study (59). The effect of BCAA supplementation on serum albumin concentration may be more effective in the early stages of cirrhosis than in the advanced stage, which could enhance total hepatic parenchymal volume (60-62).

Accelerated fat oxidation and a catabolic state after fasting are frequently observed in cirrhotic patients, which can be presented by a decrease in respiratory quotient (RQ) (63). A late evening snack containing BCAA was shown to improve RQ, nutritional state and glucose intolerance (63,64). Since BCAAs have a higher energy efficiency than glucose or fatty acids, BCAAs may be the preferred nutrients for cirrhotic patients (65).

The guidelines of the European Society for Clinical Nutrition and Metabolism and the Study Group for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis of the Ministry of Health, Labour and Welfare of Japan recommend BCAA supplementation in the treatment of advanced cirrhosis due to those preferential effects of BCAAs (1,66,67).

BCAA for HE

HE is a major and serious complication of advanced cirrhosis associated with decreased QOL in those patients, and often shows recurrence. Increased blood ammonia is usually found in HE patients, and ammonia is a pathogenic factor for HE development (68). BCAAs are used for the treatment of HE especially in cirrhotic patients, with preferential effects in most cases. The effects of BCAAs are not due to decrease in blood ammonia levels, but is thought to be due to the correction of a decreased Fischer ratio in patients with HE. HE frequently occurs in advanced cirrhotic patients after gastrointestinal bleeding, which is possibly associated with an absence of Ile and an abundance of Leu in hemoglobin molecules. The blood proteins with imbalanced BCAAs are absorbed from the gut lumen, leading to HE by way of BCAA antagonism (69).

A systematic review showed that BCAAs appeared to be beneficial on HE without adverse events (70,71). In contrast, two randomized studies showed that BCAAs did not clearly prevent HE in advanced cirrhotic patients (54,55). Furthermore, postoperative BCAA supplementation did not prevent the development of postoperative HE (72). Recently, a randomized, double-blind, multicenter study found that the supplementation of BCAAs did not reduce the recurrence of HE, although minimal HE can be prevented and muscle mass reduction can be recovered (73). Moreover, a systematic review showed that oral but not intravenous supplementation of BCAAs improved HE development (74). Non-absorbable disaccharides, which is much cheaper than BCAAs, have been shown to improve the development of HE and prevent overt HE, suggesting that non-absorbable disaccharides should be used for HE first, with BCAAs considered as the second line treatment (74). A meta-analysis showed that oral supplementation of BCAAs in patients with cirrhosis inhibited manifestations of HE especially in patients with overt HE rather than in those with minimal HE (66). Thus, oral administration of BCAAs, especially in combination with non-absorbable disaccharides, should be the treatment of choice in cirrhotic patients with HE (1).

Sarcopenia

Sarcopenia is an age-related progressive loss of skeletal muscle volume that leads to muscle weakness (75), and is associated with poor prognosis in patients with cirrhosis (76-78). Sarcopenia may be due to reduced muscle protein synthesis (79,80), and deficiencies in essential amino acids including BCAAs are thought to contribute to these processes (81,82). For example, Leu can stimulate mTOR signaling including S6K1 and 4E-BP1, leading to translation of mRNAs encoding ribosomal proteins (83,84), as well as in older rats (85). A recent clinical study showed that mTOR signaling is impaired and autophagy is increased in cirrhotic patients, and that these alterations can be reversed by supplementation with Leu-enriched BCAAs (86).

In clinical settings, supplementation with BCAAs, especially Leu, may increase skeletal muscle loss by activating mTOR signaling (86,87). However, the improvements in muscle volume were limited only to patients who showed improvements in metabolic parameters (87). Nutritional intervention with high-protein diets in elderly individuals, however, showed negative results (79,88). A recent study suggested that the effect of BCAA supplementation may be strengthened by light exercise, which upregulates amino acid transporter in skeletal muscle (89), and a prospective study also showed

that BCAA supplementation and exercise had beneficial effects in cirrhotic patients (90). BCAA supplementation for sarcopenia in cirrhotic patients should therefore be combined with adequate exercise.

Insulin resistance

Insulin resistance is often observed in patients with chronic hepatitis C virus (HCV) infection, which are thought to be associated with various complications, such as steatosis, disturbances in glucose metabolism, and hepatocarcinogenesis (91). BCAAs, especially Leu and Ile, were shown to have beneficial effects on glucose metabolism (92). It has been revealed that BCAAs directly act on insulin target organs, such as adipose tissue, skeletal muscles, and the liver (93). Intravenous administration of BCAAs was shown to decrease plasma glucose levels in advanced cirrhotic patients (94), and oral BCAA supplementation was shown to reduce both blood glucose levels (95,96) and insulin resistance in male patients with cirrhosis (31,97). Furthermore, long-term BCAA administration was reported to improve glucose tolerance in patients with nonalcoholic steatohepatitis (NASH)-related cirrhosis, suggesting that long-term BCAA may be an effective treatment for NASH (98). A randomized study showed that BCAA treatment decreased HbA1c concentrations and improved insulin resistance in patients with chronic hepatitis C (99).

BCAA in the prevention and treatment of HCC

Prevention of HCC by BCAA

HCC usually develops in patients with chronic liver diseases, especially liver cirrhosis. Chronic inflammation and fibrosis are thought to be the major mechanisms for the development of HCC, with chronic hepatitis B virus (HBV) or HCV infection being the leading cause of HCC. Although viral eradication is likely the most effective strategy for preventing the development of HCC in patients with chronic HCV infection (100), elderly patients and patients with advanced liver fibrosis were found to develop HCC even after complete eradication of HCV by direct-acting antivirals (101). Nucleos(t)ide analogs have been found to strongly suppress viral replication in patients with chronic HBV infection, significantly inhibiting the development of HCC. However, hepatocarcinogenesis can still be observed in patients with undetectable HBV-DNA but high levels of serum HBV surface antigen (102). Therefore, other supportive therapies are needed to suppress HCC development in those patients.

Inhibition of HCC cell proliferation by BCAA *in vitro*

Early *in vitro* studies showed that increased BCAA/AA ratios (103) in the medium inhibited the proliferation of HepG2 liver tumor cells. BCAAs were found to decrease the expression of insulin-like growth factor-1 (IGF-1) receptor on HepG2 cells, leading to a decrease in insulin-mediated proliferation of HepG2 cells (104). In the presence of high insulin concentrations, BCAAs were also found to reduce the expression of vascular endothelial growth factor (VEGF) by HepG2 cells, an effect mediated by shortening of VEGF mRNA (105). Although these findings suggest that BCAAs directly inhibit the growth of HCC cells, studies are needed to show whether BCAAs can clinically inhibit tumor growth inhibition.

BCAAs were shown to reduce the expression of a cancer stem cell marker, epithelial cell adhesion molecule, via the mTOR pathway, thereby increasing tumor sensitivity to 5-flourouracil (106). Clinical trials showed that BCAA supplementation synergized with acyclic retinoid (107) or sorafenib (108) in tumor treatment, suggesting that combination of BCAAs and anticancer drugs can potentiate the antitumor effects of the latter.

Prevention of HCC development in animal models

Obese diabetic rats spontaneously develop liver tumors. BCAA supplementation was shown to inhibit the development of preneoplastic lesions in these rats, an effect mediated by the suppression of VEGF expression (109). BCAAs showed similar antitumor effects in obese diabetic mice (110).

BCAAs in clinical trials

A report from Japan revealed that BCAA supplementation reduced the development of HCC in obese [body mass index (BMI) >25 kg/m^2] cirrhotic men and in those with alpha-fetoprotein levels >20 ng/mL (111). Another Japanese study also showed that BCAA supplementation (for longer than 6 months) significantly reduced HCC occurrence while enhancing event-free survival rates in Child-Pugh grade A cirrhotic patients (112). Those results are coincided with the preferential antitumor effects observed in animal models. Although there are no other data showing that BCAAs suppress hepatocarcinogenesis in cirrhotic patients, BCAA supplementation is thought to have beneficial effects

on the suppression of the liver cancer development, an effect that may be associated with improvements in insulin resistance and/or the suppression of VEGF expression.

BCAA administration as supportive therapy during treatment of HCC

BCAA supplementation in patients undergoing liver resection for HCC resulted in a shorter hospital stay and rapid improvements in liver function after surgery (113). In addition, BCAA supplementation was found to increase protein metabolism and suppress progression to liver cirrhosis after hepatectomy for HCC (114). A recent randomized controlled trial showed that preoperative administration of BCAAs before liver resection for HCC resulted in a lower frequency of ascites and higher serum albumin concentrations postoperatively (111). BCAA supplementation also suppressed early recurrence after liver resection for HCC (115).

In contrast to these findings, one report showed that pre-, peri-, and post-postoperative supplementation with BCAAs did not reduce tumor recurrence rate or improve overall survival after liver resection (116). Despite these findings, the results of most studies indicate that BCAA supplementation has beneficial effects following liver resection.

Recent studies have assessed the effects of BCAA supplementation as supportive therapy during treatment for HCC. Patients with HCC are frequently treated by radiofrequency ablation (RFA) or transcatheter arterial chemoembolization (TACE). BCAA supplementation in patients undergoing RFA has been shown to maintain patient QOL (general health, physical functioning and social functioning) (117), liver function and serum albumin levels (118), and to improve overall survival and recurrence-free survival (119). BCAA supplementation showed similar results in HCC patients undergoing TACE (120) or radiotherapy (121).

Collectively, BCAA administration has various benefits, such as preventing the development of HCC in patients with liver cirrhosis, improving or maintaining liver reserve functions during invasive treatments for HCC, and enhancing overall survival after curative treatment for HCC. However, BCAA formulations are expensive and most reports to date have been from Japan. It will be necessary to analyze the cost effectiveness of BCAA supplementation in patients with liver cirrhosis or HCC, as well as to assess the effects of BCAA supplementation in non-Japanese patient populations.

Conclusions

BCAAs have been shown to have various biological effects, including the promotion of protein synthesis and hepatocyte proliferation, simulation of immune systems, improvement of insulin resistance, inhibition of liver cancer cell proliferation and neovascularization. All of these findings indicate that BCAAs may have beneficial effects on the management of patients with chronic liver diseases with/without HCC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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