Branched-Chain Amino Acids: Metabolism, Physiological Function, and Application

Therapeutic Use of Branched-Chain Amino Acids in Burn, Trauma, and Sepsis[1,2]

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ABSTRACT Various experimental studies conducted in the 1970s demonstrated, at least in the physiological situation, the anabolic and/or anticatabolic properties of branched-chain amino acids (leucine, valine, isoleucine) or their ketoacid derivatives. This led to several clinical studies in the late 1970s and early 1980s that aimed to evaluate the potential benefits of BCAA supplementation in nutritional support of the critically ill. The data on burn, trauma, and sepsis are, however, far from convincing. Besides significant discrepancies in their results and the fact that most of these studies involved very small populations of patients, few of them meet the current standards of therapeutic evaluation. However, some positive results in specific studies suggest that the underlying concept may be correct but that interpretation has been faulty. Indeed, we know now that while the BCAAs possess regulatory properties on protein metabolism, leucine is by far the most potent, while isoleucine and valine are inefficient. However, in the above-mentioned studies, BCAA-supplemented nutrition very frequently supplied almost equivalent amounts of all 3 BCAAs. Moreover, several studies were performed without adequate basal nutritional support, which most probably hampered the correct metabolic utilization of these amino acids. Taken together, these factors mean that the demonstrations of BCAA efficacy were fortunate in the least. In contrast, more recently, leucine was demonstrated to positively affect protein synthesis in an experimental model of sepsis or burn. In parallel, 2 prospective controlled trials of BCAA supplementation in septic patients also demonstrated an improvement in patients' nutritional status and outcome. Thus, we should abandon the concept of BCAA-supplemented nutrition for a more promising leucine-supplemented nutrition that requires further evaluation. J. Nutr. 136: 308S–313S, 2006.

KEY WORDS: • *leucine* • *valine* • *critical care* • *injury*

The metabolic response to acute injury is mainly represented by an increase in metabolic rate and a reprioritization of body fuel utilization in favor of the visceral organs. This is demonstrated by accelerated metabolic rates, increased nitrogen loss and loss of lean body mass, stimulated acute-phase protein synthesis in the liver, and abnormalities in lipid and carbohydrate metabolism. If left unchecked, this metabolic response to stress could lead to malnutrition, which will worsen the stress situation by increasing the patient's susceptibility to infection. At first, this unfavorable change is related to the mobilization and progressive depletion of the body's protein stores (1). Hence, a catabolic insult such as trauma, burn, or sepsis induces a marked generalized net protein catabolism in the muscle, as indicated by increased nitrogen loss and excretion of urinary 3-methylhistidine (3MH,[4] a marker of myofibrillar catabolism) (2). Depending on the catabolic insult and its severity, this loss in muscle protein results from decreased, normal, or even increased protein synthesis, which in the latter case, remains insufficient to compensate for higher proteolysis. This accelerated protein breakdown is associated with inhibited uptake of amino acids (AAs) by the muscles, leading to an increased flux of amino acids from the periphery to the liver. In parallel, hepatic uptake of AAs is stimulated and protein synthesis and gluconeogenesis in the liver are enhanced (1). The alterations in nitrogen and protein metabolism represent a major threat for the organism, as demonstrated by the relationship between loss of lean body mass and morbidity or mortality (3). Therefore, a therapy able to promote protein anabolism or slow down protein degradation would constitute a major step forward.

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[4] Abbreviations used: 3MH, 3-methylhistidine; AA, amino acids; BSA, body surface area burned; eIF4, eucaryote initiation factor 4; ICU, intensive care unit; Ile, isoleucine; Leu, leucine; mTOR, mammalian target of rapamycin; TPN, total parental nutrition; Val, valine.

In this context, experiments have shown that the branched-chain amino acids (BCAA) leucine (Leu), isoleucine (Ile) and valine (Val) promote muscle protein synthesis and reduce protein catabolism (4–8). These observations have led to several experimental and clinical studies in stress situations conducted to evaluate the possible clinical benefit of BCAA supplementation. In this review we will focus our attention on burn injury, nonsurgical trauma, and sepsis.

The experimental basis of BCAA supplementation in stress situations

In 1972, Odessey and Goldberg (4) showed in isolated muscle preparation that BCAAs appeared to display regulatory properties on AA metabolism in the muscle. This was followed in 1975 by 2 separate studies, which independently pointed to the possible regulatory role of BCAAs on muscle protein turnover. Fulks et al. (5) developed a simple method for measuring protein turnover in the isolated diaphragm. They used this model to investigate the influence of factors known to be regulators of protein synthesis and degradation, such as insulin and AAs. These authors demonstrated that at 5-fold plasma concentrations, the BCAAs alone decreased protein catabolism (−26%) and stimulated protein synthesis (+23%) as efficiently as a complete AA mixture, but that, in contrast, the same AA mixture but devoid of BCAAs remained ineffective. At the same time, Buse and Reid (6) proposed a regulatory role for BCAAs on protein metabolism: they postulated that the wasting of muscle protein in severe stress or in uncontrolled diabetes was related to the depletion of intracellular BCAAs induced by stimulated oxidation of these AAs. Using isolated rat hemi-diaphragm, they demonstrated that a mixture of the 3 BCAAs did indeed stimulate protein synthesis. Surprisingly, they also pointed to the fact that, when tested separately, only leucine was effective, but this result does not seem to have been fully taken into account during the development of the BCAA concept (see below). In additional experiments, these authors also demonstrated that leucine exerted an inhibitory effect on protein degradation.

In the following years, several studies aimed at improving our understanding of the metabolic effects of BCAAs, and more specifically, at identifying separate effects on protein synthesis and protein degradation. Using isolated diaphragms and atrial muscles, Tischler et al. (7) showed that increasing concentrations of leucine (over the range observed in plasma) decreased proteolysis more than they stimulated synthesis: at low concentrations, leucine stimulated protein synthesis without reducing proteolysis, whereas at higher concentrations the absolute decrease in proteolysis was greater than the absolute increase in protein synthesis. They observed that changes in intracellular leucine were correlated with changes in protein synthesis and degradation. They also demonstrated that a 95% inhibition of leucine transamination by cycloserine did not affect the ability of leucine to stimulate protein synthesis. Conversely, while cycloserine was by itself without effect on protein degradation, it completely blocked the effect of leucine on proteolysis. Lastly, these authors observed that α-ketoisocaproic acid, the product of leucine transamination, was ineffective on protein synthesis but inhibited proteolysis. Of note, this inhibitory effect in atrial and in skeletal muscles may possibly occur through different mechanisms, because the ketone bodies were ineffective in the diaphragm whereas, in the heart, Chua et al. (8) demonstrated that not only leucine and α-ketoisocaproic acid but also other metabolites of BCAA that are oxidized in the citric acid cycle (such as acetoacetate, acetate and propionate) were able to inhibit proteolysis.

BCAA supplementation in burn injury

Burn injury seems to represent a very specific situation, since the pathophysiological mechanisms involved in the metabolic response to this insult may differ from the common paradigm. For example, Lang et al. (9) studied the influence of different catabolic stresses on the expression of myostatin, a negative regulator of muscle mass potentially involved in muscle loss in response to injury. Myostatin mRNA was increased 3- to 4-fold in the gastrocnemius after a 30% burn while neither endotoxin nor peritonitis significantly altered myostatin mRNA. This response was blocked by a glucocorticoid receptor antagonist but not by tumor necrosis factor binding protein (TNFBP), which antagonizes the action of this cytokine. Burn injury is also a very specific situation as it has been demonstrated to be surprisingly responsive to a large array of anabolic factors (insulin, growth hormone, IGF-1, β-blockers, among others) (10). Thus, burn injury deserves to be considered separately from other trauma situations.

Experimental studies. The ability of BCAAs to dampen protein loss in burn injury was not evident from the outset, as suggested by an initial study by Odessey and Parr (11). They used a model of mild thermal injury in young rats that associated increased protein breakdown limited to the injured limb with preserved protein synthesis. In isolated muscle from the unburned limb, leucine displayed its normal inhibitory effect on protein degradation; however, in muscle from the burned hind limb, leucine was ineffective. Taking into account the relative proportionality between injury severity and metabolic response, this did not predict favorable results in severe burns.

The potential benefit of in vivo BCAA supplementation was further tested in 2 experimental studies. In severely burned (30% full-thickness flame burn) guinea pigs receiving enteral nutrition, Mochizuki et al. (12) studied the effect of various protein loads (whey protein, 10 to 30%) supplemented or not with BCAAs (21.5% or 50%; 39% leucine). On d 14 post-burn, the 10% groups were severely malnourished, and the 30% protein BCAA-supplemented group displayed digestive intolerance. In the 20% groups, BCAA supplementation did not improve weight gain, carcass and muscle (gastrocnemius) weights, albumin and cumulative nitrogen balance.

In rats subjected to 15% full-thickness scald burns and receiving total parental nutrition (TPN) Mori et al. (13) compared 2 diets with 45% (molar ratio Ile/Leu/Val: 1/2/1) and 21% (molar ratio Ile/Leu/Val: 1/1.9/1.3) BCAA. They observed a faster improvement in hepatic glycogen and protein and in muscle protein contents as well as in protein catabolism (assessed by the measurement of 3MH urinary excretion) in the BCAA-supplemented group. Nitrogen balance remained unaffected in these experiments.

The comparison between these 2 studies is difficult, because in addition to the difference in animal models (rat vs. guinea-pig), the severity of the injury and the mode of nutrition also differed. The importance of this last point is underlined by the demonstration that requirements for the different BCAAs vary according to the route of feeding (14). However, these studies do not provide a strong rationale for the use of BCAAs in burn injury.

Clinical studies. Only 3 studies in burn patients are available. First, Manelli et al. (15) administered BCAA-supplemented (41%, molar ratio Ile/Leu/Val: 0.9/1.2/1.1) or conventional (22% BCAA; molar ratio Ile/Leu/Val: 1/2/1.1) parenteral nutrition in 22 patients with 35% (20–90) [mean (range)] full-thickness burn. The patients were studied for 5 d during the immediate post-injury period and received similar nitrogen ($0.2\ g \cdot kg^{-1} \cdot d^{-1}$) and calorie ($\approx 35\ kcal \cdot kg^{-1} \cdot d^{-1}$)

supplies. Although plasma urea and creatinine, urinary nitrogen loss, and cumulated nitrogen balance were similar between the 2 groups, BCAA supplementation led to a significant decrease in the urinary 3MH:creatinine ratio, evidencing an improvement in protein catabolism. Positive results were also obtained by King and Power (16). These authors studied, for nearly 18 d post-burn, 14 patients receiving, via the enteral route, a standard regimen (group C, $n = 6$) or a diet enriched either with 31% BCAAs (molar ratio Ile/Leu/Val: 0.9/3.1/1.0; group A, $n = 4$) or the same amounts of isoleucine and valine with 65% of leucine replaced by ketoisocaproate (group B, $n = 4$). Neither nitrogen balance nor serum albumin or transferrin concentrations were significantly affected by the supplementations. Group A displayed decreased 3MH urinary excretion, suggesting reduced protein breakdown. This cannot be considered as full confirmation of the results of Manelli et al. (15), given the very limited number of patients and the heterogeneity in burn severity (body surface area burned [BSA]: group A: 32.0 ± 7.2% and group C: 40.3 ± 15.4%; ns). Additionally, this study suggested that ketoisocaproate supplementation was ineffective.

However, Yu et al. (17) failed to demonstrate a BCAA supplementation–related benefit. They studied 12 patients (BSA: 36 ± 5% burn) at an average of 25 d post-burn using a crossover experimental design. In each 2–4-d nutrition period, the patients received either a BCAA-enriched (44%, molar ratio Ile/Leu/Val: 1/1.75/0.8) or a conventional (20% BCAA) enteral feeding. A kinetic study of leucine metabolism was performed at the end of each nutrition period. There were no differences in protein synthesis or degradation between the 2 periods. Leucine flux and oxidation increased significantly during BCAA supplementation whereas apparent nitrogen balance was not affected. It should be noted that BCAA supplementation was associated with a 2-fold increase in the plasma concentrations of these AAs.

Although no definitive conclusion on the effectiveness of BCAAs can be drawn from these studies, the difference in delay between injury and nutritional supplementation is another factor that must be taken into account. As suggested by Mori et al. (13), the beneficial effects of BCAAs could be most marked during the initial post-injury period. Another aspect that we will discuss below is the importance of the relative supply of leucine compared with the other BCAAs.

BCAA supplementation in trauma and ICU patients

Studies on BCAA supplementation in experimental surgical trauma or clinical elective surgery are detailed elsewhere (18) and therefore will not be considered here.

To our knowledge, there are no available data on the effects of BCAA supplementation in experimental nonseptic non-surgical trauma injury.

Among the 7 available studies performed on trauma patients, 6 administered BCAA-supplemented nutritional support and 1 administered leucine-supplemented nutritional support. Three concluded that BCAA supplementation was beneficial. However, interpretation of the results is made difficult by the heterogeneity of the patients included in these studies (multiple trauma, surgery, etc.) and by the absence in some studies of a balanced nutritional support or detailed composition of the support provided.

Schmitz et al. (19) were the first to conclude as no effect on the utility of BCAA supplementation in a study of 30 intensive care surgical patients who were randomized to receive parenteral glucose and amino acids (45% vs. 10% BCAA: molar ratio Ile/Leu/Val: 0.8/1.1/1). The characteristics of the patients were not indicated, but based on the level of nitrogen excretion, they do not appear to have been clearly hypercatabolic or even to have required parenteral nutrition. Vander Woude et al. (20) also failed to demonstrate a benefit associated with BCAA administration in a randomized crossover study of BCAA supplementation (4 d at 44.6% BCAA vs. 4 d at 19% BCAA, molar ratio of individual BCAA unknown) in 10 critically ill patients. It is doubtful that any positive effect of parenteral nutrition could have been expected in this group of patients with a 70% mortality. Moreover, their conclusion is based only on the absence of significant difference in nitrogen balance or in femoral amino acid arteriovenous differences (leg blood flow was not evaluated). Lennmarken et al. (21) studied 16 polytrauma patients receiving 40 kcal $\cdot$ kg^{-1} $\cdot$ d^{-1} parenterally as fat and 20% glucose or leucine (57 g/d) dissolved in 10% glucose and fat. Unsurprisingly with such an unbalanced nutritional support, they failed to observe a significant advantage of leucine supplementation. The largest study with no effect of BCAA supplementation is that of Vente et al. (22) conducted on 101 trauma and septic patients. In this prospective, randomized, double-blind trial, patients received total parental nutrition (TPN; mean: 33.5 kcal $\cdot$ kg^{-1} $\cdot$ d^{-1}, 0.17 gN $\cdot$ kg^{-1} $\cdot$ d^{-1}) for 7 d with either 15.6% or 50.2% BCAAs (molar ratio Ile/Leu/Val: 1/1/1). They did not observe any differences in nitrogen balance or plasma proteins. Although the authors stated that the patients were stratified for stress and sepsis, this was not shown in the results. They carefully took into account the extra nitrogen supply and nonurinary loss in the calculation of nitrogen balance: in this study, this extra nitrogen supply (as perfusion of plasma or albumin solution) was particularly elevated, and has been suggested to be a confounding factor when comparing the effects of 2 AA supplementations (23). Additionally, this invalidated their negative conclusions based, in part, on plasma protein concentrations.

Three studies claimed that they observed positive results with BCAA supplementation. Pelosi et al. (24) compared during a 10-d period 2 parenteral nutrition solutions consisting of 25% glucose and either 25% or 43% BCAA-enriched AA solutions (molar ratio Ile/Leu/Val: 0.8/1.4/1) in 22 polytrauma patients with varying degrees of trauma and sepsis. They observed an improvement in cumulative nitrogen balance and 3MH excretion. Cerra et al. (25) very optimistically concluded that "metabolic support of the stress response in ICU patients has become a clinical reality" based on the results of their study in 32 surgical and polytrauma patients. In this study, patients were randomized into 4 groups to receive for 7 d either 30 kcal $\cdot$ kg^{-1} $\cdot$ d^{-1} (glucose) and 1 gAA^{-1} $\cdot$ kg^{-1} $\cdot$ d^{-1} (15 or 50% BCAA) or 37 kcal $\cdot$ kg^{-1} $\cdot$ d^{-1} (glucose and lipids) and 1.5 gAA^{-1} $\cdot$ kg^{-1} $\cdot$ d^{-1} (20 or 47% BCAA). Their data indicate that BCAAs reduce nitrogen loss and that this effect is proportional to BCAA load. Although the injury severity of the patients was not indicated, the data suggest that they were only mildly catabolic, with 3 of the 4 groups of patients already presenting positive nitrogen balance on d 3. The last study by Echenique et al. (26) did not evaluate the benefits associated with prolonged BCCA supply but followed the metabolic events associated with a 24 h-supplementation. These authors studied 5 critically ill patients under TPN (0.18 gN^{-1} $\cdot$ kg^{-1} $\cdot$ d^{-1} and 21 kcal $\cdot$ kg^{-1} $\cdot$ d^{-1}) in a 2 $\times$ 24 h crossover trial. Patients received either 15.6% or 50% BCAA-containing solution (the exact composition of the BCAA mixture is unknown), and leucine kinetics were studied. Although the improvement in muscle protein synthesis and the decrease in protein degradation were not significant with BCAAs, a significant improvement in muscle protein balance was observed during the BCAA period.

Large, well-conducted, prospective trials of BCAA supplementation are thus needed in the trauma situation before conclusions can be reached.

BCAA *supplementation in septic patients*

BCAA in experimental sepsis. The efficiency of BCAA supplementation during sepsis has been repeatedly evaluated.

From a pathophysiological point of view, Hasselgren et al. (27) demonstrated that the ability of leucine and ketoisocaproate to modulate protein metabolism was significantly affected by sepsis. Using the model of incubated isolated muscle from rats made septic by cecal ligation and puncture, they observed that the concentration of leucine required to stimulate protein synthesis was 2-fold higher during sepsis compared with normal muscle. However, protein breakdown was unaffected by leucine or ketoisocaproate even at very high concentrations. Of note, these results were not the consequence of variations in AA availability because the intracellular concentration of leucine was similar in septic and normal muscles.

Some in vivo studies must be considered with caution because BCAAs were supplied either alone or as part of a complete amino acid solution but without carbohydrates or lipids. For example, Blackburn et al. (28) evaluated the effects of BCAA in a model of enteral nutrition during bilateral septic femoral fracture in rats. Unsurprisingly, AA (25% BCAA)-supplemented rats fared better than fasted animals, but doubling the BCAA supplementation (50% BCAA) did not prove of further benefit, except for an improvement in hepatic nitrogen content and visceral protein synthesis. Interestingly, Nachbauer et al. (29) showed, in guinea pigs submitted to cecal ligation but without puncture, that BCAAs associated with a glucose supply induced a reduction in protein degradation, as indicated by a reduction in 3MH excretion. The 3MH: creatinine ratio was inversely correlated to the amount of BCAA and, importantly, of the 3 BCAAs only the amount of leucine infused correlated with weight-adjusted 3MH excretion.

In vivo studies with complete balanced parenteral nutrition support are rather contradictory. Two studies from Fisher's group in rats submitted to cecal ligation and puncture are really confusing because one concluded that the improvement in nitrogen balance with BCAA in sepsis reflected increased protein synthesis and/or reduced degradation in tissues other than skeletal muscle (30) whereas the other concluded that this effect was not caused by improved hepatic protein balance (31). It should be noted that neither of these 2 studies measured 3MH excretion. In the same model of cecal ligation and puncture in rats, 3 studies gave more favorable results. Mori et al. in a first study (32) observed a significant improvement in nitrogen balance and a decrease in mortality with BCAA-supplemented (36%, molar ratio Ile/Leu/Val: 1/1.75/0.8) TPN compared with standard (21% BCAA; molar ratio Ile/Leu/Val: 1/1/1) TPN. In a second study, these authors (33) used a higher enrichment in BCAA (45%) but compared 2 formulations, one with 50% BCAA as leucine (molar ratio Ile/Leu/Val: 1/1.75/0.8) and the other as valine (molar ratio Ile/Leu/Val: 1/1/2.2). Valine was associated with increased nitrogen loss and a dramatic increase in plasma valine, but this was not observed with leucine supplementation which was associated with an increase in muscle protein synthesis. An improvement in muscle protein metabolism was also demonstrated by Kawamura et al. (34) who compared 25% and 50% BCAA-enriched TPN at a fixed molar ratio (Ile/Leu/Val: 1/1/1) and showed a marked improvement in muscle mass, nitrogen balance, and 3MH excretion with 45% BCAA.

Thus, in experimental models of sepsis, BCAA supplementation seems to favor nitrogen economy. This is probably associated with a reduction in protein loss at the muscle level and/or an improvement in visceral protein synthesis.

BCAA supplementation in septic patients. BCAA supplementation during sepsis was first studied by Bower et al. (35) in 37 patients receiving either conventional or 2 different BCAA-enriched TPN. However, defects in the study protocol preclude definite conclusions other than the fact that the first of the 2 TPN solutions tested, which contained a majority of valine, was ineffective. Freisz et al. (36) also addressed this question in 19 septic patients, but the TPN solutions were markedly hypocaloric, which is a serious limitation to the favorable conclusion of these authors.

Two more recent studies, however, seem to indicate that there is a strong rationale for BCAA-supplemented nutrition in septic patients. In a prospective, randomized, controlled trial, Jimenez Jimenez et al. (37) studied 80 patients with peritonitis using clearly defined criteria. They compared 2 isocaloric (1800 kcal/d, 60% glucose) isonitrogenous (12 gN/d) TPNs containing either 22.5% or 45% BCAA (molar ratio Ile/Leu/Val: 0.8/1.4/1). These authors noted a significant improvement in nitrogen balance, in 3MH excretion and in short half-life visceral proteins with BCAA supplementation; however, mortality remained similar between the 2 groups. More recently, Garcia de Lorenzo et al. (38) performed a multicenter, prospective, randomized trial in 69 intensive care patients with sepsis who were unable to receive enteral nutrition. Patients were randomized into 3 groups to receive isocaloric (24 kcal $\cdot$ kg^{-1} $\cdot$ d^{-1}) TPN containing either 1.5 g AA^{-1} $\cdot$ kg^{-1} $\cdot$ d^{-1}with 23% or 45% BCAA (molar ratio Ile/Leu/Val: 0.8/1.4/1), or 1.1 gAA^{-1} $\cdot$ kg^{-1} $\cdot$ d^{-1} with 45% BCAA (molar ratio Ile/Leu/Val: 0.8/1.4/1). Although the authors did not observe any differences between groups in terms of nitrogen balance, there was a significant improvement in short half-life visceral proteins and in mortality in the 2 BCAA-supplemented groups.

BCAA *concept or leucine concept?*

As already mentioned, experimental studies have emphasized the ineffectiveness of valine and isoleucine in modulating nutritional status in stress situations. As early as 1975, Buse and Reid (6) showed that, even in normal situations, only leucine was effective. This was confirmed by Mori et al. (33) who compared 2 formulations, one mainly enriched with leucine and the other with valine, in burned rats. Clinical studies have provided further evidence. For example, Bower's study (35) in septic patients showed that BCAA supplementation with a majority of valine was ineffective. Similarly, Gore and Wolfe (39) showed in critically ill patients that an alanine-glutamine-valine supplement was ineffective. Note that positive results were most frequently observed with AA solutions containing a higher molar ratio of leucine.

In proportion with our progress in understanding the involvement of leucine in the regulation of protein synthesis (40,41), various studies have explored the alterations of this response in stress situations. Two recent experimental studies in burned rats further support the utility of leucine supplementation in such stress situations. In a model of partial thickness thermal injury to the ear in rabbits, Zhang et al. (42) compared the effects of a standard AA solution, leucine alone, or a leucine-supplemented (at 2 concentrations: 25 and 35%) AA solution at d 7 post-burn. They demonstrated an anabolic effect on skin and muscle proteins of leucine-supplemented AA solution but not of leucine alone, and this effect was more marked for the 35% solution. This ability of leucine to promote protein synthesis was also demonstrated by Lang et al. (43) in a model of 40% full-thickness scald burn in rats. These authors observed that burn injury leads to a redistribution of the translation initiation factor eIF4E with increased binding of this

factor to its repressor 4E-BP1 and decreased binding to eIF4G; it also leads to a decrease in the phosphorylation of several proteins involved in the regulation of protein synthesis, such as mammalian target of rapamycin (mTOR), S6 kinase 1, S6, and eIF4G. They demonstrated that leucine reversed these alterations in eIF4E distribution and in mTOR, S6, and eIF4G phosphorylation in heart muscle.

Thus, while data supports the notion of a relative decrease in the anticatabolic effect of leucine in stress situations, it preserves part of its effectiveness. This leucine concept deserves to be evaluated in large, randomized, controlled trials in patients receiving truly adequate nutritional support.

Conclusion and ideas for future research

First, leucine is part of the pharmaconutrients family (which also includes glutamine, arginine, and ornithine α-ketoglutarate), i.e., nutrients that, by modulating cell signaling, exert anabolic/anticatabolic functions when provided in sufficient amounts, with these effects occurring independently of the nutritional value of the supplement. This means that leucine supplementation should be given in addition to, and not as a replacement of part of, a sufficient and balanced nutritional support (44). No effects of BCAA have been logically obtained in studies providing extravagantly high amounts of BCAAs and/or hypocaloric and/or low nitrogen supplies. This has marked the death of the concept of BCAA-enriched nutrition (45,46).

Second, as underlined above, only leucine and not the other BCAAs exhibits pharmacological properties. Leucine, valine, and isoleucine compete for cell transport and metabolism (47). Imagine a regimen providing 20% BCAAs with an Ile/Leu/Val ratio of 1/2/1 and another regimen, BCAA-enriched, providing 40% BCAAs but with a ratio of 1.5/1/1.5: the 2 solutions actually contain the same amount of leucine and the so-called BCAA-enriched solution is relatively less rich in leucine than the standard diet. It is clear that further studies must consider a true leucine-enriched regimen.

Third, as mentioned in the introduction, the response to stress is associated with maintained, decreased or even increased protein synthesis with comparatively higher protein catabolism, which suggests different underlying pathophysiological mechanisms. It is worth noting that in some studies performed in stress situations (e.g., see Biolo et al. [48]), muscle BCAA levels are increased and not decreased. In this context, the rationale for BCAA supplementation is hard to establish.

Finally, the adaptive responses to stress of BCAA and glutamine metabolism in muscle are closely related. Glutamine is a potent regulator of protein turnover and its muscle concentration is consistantly decreased following trauma (49). There is a clear gap between our knowledge of the pathophysiology and our therapeutic options. Further insight into the pathophysiological response to stress and differences according to type of stress is thus required to further improve the nutritional support of our patients.

On this basis, we hope that future well-conducted studies will allow us to claim: "The BCAA king is dead, long live the leucine king."

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