Relation Between Glutamine, Branched-Chain Amino Acids, and Protein Metabolism

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The branched-chain amino acids (BCAAs; valine, isoleucine, and leucine) are the major nitrogen source for glutamine and alanine synthesis in muscle. Synthesis of glutamine, alanine, and BCAA use is activated in critical illnesses such as in sepsis, cancer, and trauma. The use of glutamine often exceeds its synthesis, resulting in the lack of glutamine in plasma and tissues. In critical illness, resynthesis of BCAA from branched-chain keto acids is activated, particularly in hepatic tissue. The BCAA released to circulation may be used for protein synthesis or synthesis of alanine and glutamine. Glutamine and/or alanine infusion has an inhibitory effect on the breakdown of body proteins and decreases BCAA catabolism in postabsorptive control, endotoxemic, and irradiated rats. Decreased protein breakdown also was observed when glutamine synthesis was activated by ammonia infusion. In conclusion some favorable effects of BCAA supply can be explained by its role in the synthesis of glutamine and some positive effects of glutamine exogenous supply can be explained by its effect on metabolism of BCAA. *Nutrition* 2002;18: 130–133. ©Elsevier Science Inc. 2002

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INTRODUCTION

Glutamine and the branched-chain amino acids (BCAAs) valine, leucine, and isoleucine undoubtedly have been the most frequently studied amino acids of the past three decades. Observation of activated oxidation of BCAAs and their unique metabolic properties was a rational argument leading to the employment of BCAA-enriched solutions in patients with hepatic encephalopathy, sepsis, renal failure, and trauma. However, the clinical data evaluating the effect of BCAA-enriched solutions are controversial and the clinical usefulness of BCAA has not been resolved.[1,2] The expansion in glutamine research and its therapeutic exploitation belong to the 1980s and 1990s. Decreases in plasma and the muscle glutamine pool have been found in life-threatening conditions associated with muscle wasting such as in sepsis, cancer cachexia, burn injury, and trauma.[3,4] Several studies have reported improvements in clinical outcome and nitrogen balance when glutamine, glutamine-containing dipeptides, or α-ketoglutarate are given to critically ill patients.[2,5–8]

The results of several studies performed in different laboratories including my own have clearly demonstrated the interesting relations in metabolism of glutamine and BCAA. The aim of this article is to point out the importance of those relations.

BCAA METABOLISM IN CRITICAL ILLNESS

BCAAs are essential amino acids that serve as an essential substrate and important regulator in the synthesis of body proteins and represent the major nitrogen source for glutamine and alanine synthesis in muscle. Enhanced rate of BCAA oxidation is commonly associated with the systemic inflammatory response (SIR), a host response frequently induced by severe illnesses such as sepsis, cancer, trauma, and burn injury.[9,10] The main source of BCAAs in SIR is undoubtedly lean muscle tissue. The SIR, orchestrated mainly by the hypothalamus, autonomic nervous system, and cytokines undoubtedly is, in principle, beneficial for the body. However, there are some negative effects of SIR, such as muscle wasting, that can contribute to the fatal end of disease.

The first step in BCAA catabolism (Fig. 1) is reversible transamination leading to the production of corresponding branched-chain keto acids (BCKAs). The skeletal muscle is considered the initial site of BCAA catabolism because of a high activity of BCAA aminotransferase. The BCKAs formed in this reaction then undergo oxidative decarboxylation catalyzed by BCKA dehydrogenase and/or are released into the bloodstream and then taken up by different tissues where they can be oxidized or used for resynthesis of BCAA.[11] The ability to reaminate BCKA and release the corresponding BCAAs into the bloodstream (the basis for the use of BCKA in the treatment of chronic renal failure) has been shown in brain, heart, kidneys, liver, and skeletal muscle.[12–15] It should be noted that the direction of BCAA aminotransferase reaction is determined by the BCKA dehydrogenase activity, the supply of BCAA and BCKA, and probably a number of other factors.[11] The results of several studies have indicated that favorable conditions for synthesis of BCAA from BCKA are in hepatic tissue. The liver can extract a quantity of BCKA equivalent to that released by muscle.[16] Abumrad et al.[17] found that, after infusion of ketoisocaproic acid into the gut of postabsorptive dogs, 59% of the absorbed ketoisocaproic acid was taken up by the liver and one-third of that percentage was transaminated to leucine. These observations clearly indicate that there is a cycle between the muscle and liver that enables resynthesis of BCAA from BCKA. The BCAA released from the liver to circulation may be used in skeletal muscle for protein synthesis or synthesis of alanine and glutamine.

The ability to reaminate BCAA from BCKA is markedly activated in severe illness. In hepatic tissue of endotoxemic rats or rats

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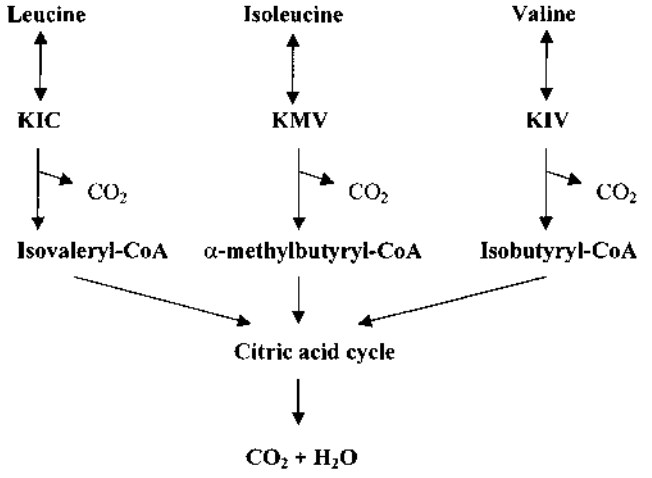

FIG. 1. Catabolism of branched-chain amino acids. CoA, coenzyme A; KIC, α-ketoisocaproic acid; KIV, α-ketoisovaleric acid; KMV, α-keto-β-methylvaleric acid.

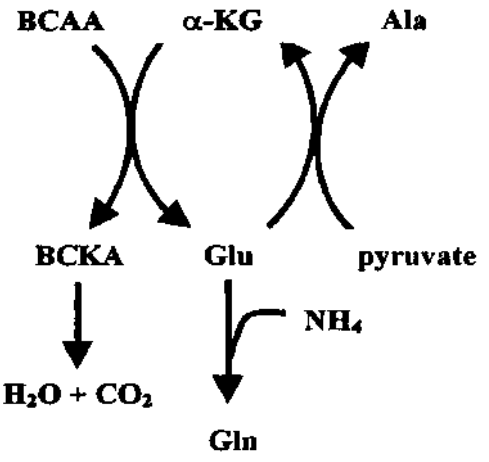

FIG. 2. Relation between Glu and Ala production and BCAA catabolism in muscle. α-KG, α-ketoglutarate; Ala, alanine; BCAA, branched-chain amino acid; BCKA, branched-chain keto acid; Gln, glutamine; Glu, ??.

treated with tumor necrosis factor-α, a significant decrease in BCKA dehydrogenase activity simultaneous with an increase in BCAA aminotransferase activity were observed.[18,19] These changes, which indicate increased capacity of hepatic tissue to reaminate BCKA to BCAA, were confirmed with the use of an isolated perfused rat liver technique by adding ketoisocaproic acid (leucine precursor) to perfusion medium. In effluent of hepatic tissue of endotoxemic rats, a significantly higher leucine concentration was detected than in controls.[19] Significant decrease in the flux of ketoisocaproic acid through hepatic BCKA dehydrogenase was observed in rats with liver cirrhosis.[20] Because SIR is commonly associated with anorexia, the activated resynthesis of BCAA in hepatic tissue should be considered an important adaptive response of the body that can resupply essential BCAAs and prevent the rapid development of negative nitrogen balance.

GLUTAMINE AND BCAA METABOLISM

BCAAs are considered essential donors of nitrogen in synthesis of glutamine and alanine in skeletal muscle. Addition of BCAAs to the perfusion medium induced significant releases of alanine and glutamine from rat hindquarters.[21] Administration of BCAA to skeletal muscle homogenates significantly increased glutamine synthetase activities.[22] Infusions of leucine into human subjects increased glutamine in blood.[17,23–25] Direct evidence that BCAAs donate their nitrogen to glutamine was provided by Golden et al. who used [^{15}N] labeling.[26]

Glutamine and alanine have important functions and the enhanced synthesis of these amino acids is essential in severe illness. Glutamine, in addition to its role in acid–base homeostasis and gluconeogenesis, acts as a "nitrogen shuttle" among organs, an important fuel for rapidly dividing cells such as enterocytes and cells of the immune system, and a precursor for the synthesis of nucleotides. Alanine is an important precursor for gluconeogenesis in liver during starvation and severe illness. It seems that the marked increase in protein degradation in skeletal muscle that provides sufficient amounts of BCAAs during SIR is essential for the synthesis of glutamine and alanine.

The demands of the body for alanine and glutamine during catabolic illness are enormous, and the increased use of glutamine in particular often exceeds its synthesis, resulting in the lack of glutamine in plasma and tissues.[4] Glutamine deficiency in severe illness is the rationale for the use of glutamine in nutritional therapy. In contrast to a marked decrease in glutamine, the decreased concentrations of BCAAs are not commonly seen in proteocatabolic illness. This phenomenon may lead to a misleading opinion that there is no lack of BCAA in stress states. The main cause of unchanged BCAA levels in severe illness is undoubtedly the enormous influx of BCAAs due to activated proteolysis and resynthesis from BCKA.

Figure 2 shows the metabolic relations between BCAA, glutamine, and alanine in metabolism and evokes a simple question: "What are the physiologic and clinical consequences of these metabolic relations?" Alanine and/or glutamine supplementation should have a significant influence on BCAA metabolism if a physiologically significant relation exists between alanine or glutamine and BCAA metabolism. This assumption was confirmed in intact and endotoxemic rats. Infusion of alanyl-glutamine (Ala-Gln) markedly decreased plasma BCAA levels, decreased leucine oxidized fraction, and improved protein balance associated with a higher decrease in whole-body proteolysis than in protein synthesis.[27] Similar changes in leucine and protein metabolism were induced by infusion of alanine or glutamine, but not of glycine. An almost identical effect of Ala-Gln infusion on BCAA and protein metabolism was observed in the whole-body irradiated rats.[28] A decrease in plasma leucine concentration during enteral glutamine administration has been reported also by others.[5,29] Decreased leucine oxidation after glutamine administration can be explained by increased glutamine oxidation that yields NADH; elevating the $NADH/NAD^+$ ratio inhibits BCKA dehydrogenase, the key enzyme in BCAA oxidation.[30]

To obtain a more complex answer concerning mutual relations between glutamine, BCAA and protein metabolism, my colleague and I also investigated the effect of activated endogenous synthesis of glutamine induced by infusion of ammonium salts.[31] Ammonium infusion increased levels of ammonia and glutamine in plasma, decreased BCAAs and alanine in plasma and skeletal muscle, and significantly decreased whole-body proteolysis and protein synthesis. Leucine oxidation was unchanged, whereas the leucine oxidized fraction, i.e., the ratio of leucine oxidation and leucine disappearance rate from blood plasma, increased significantly. These data are in agreement with observations of decreased protein turnover after glutamine and/or Ala-Gln infusion. The increase in leucine oxidized fraction demonstrates increased BCAA use for synthesis of glutamic acid and glutamine.

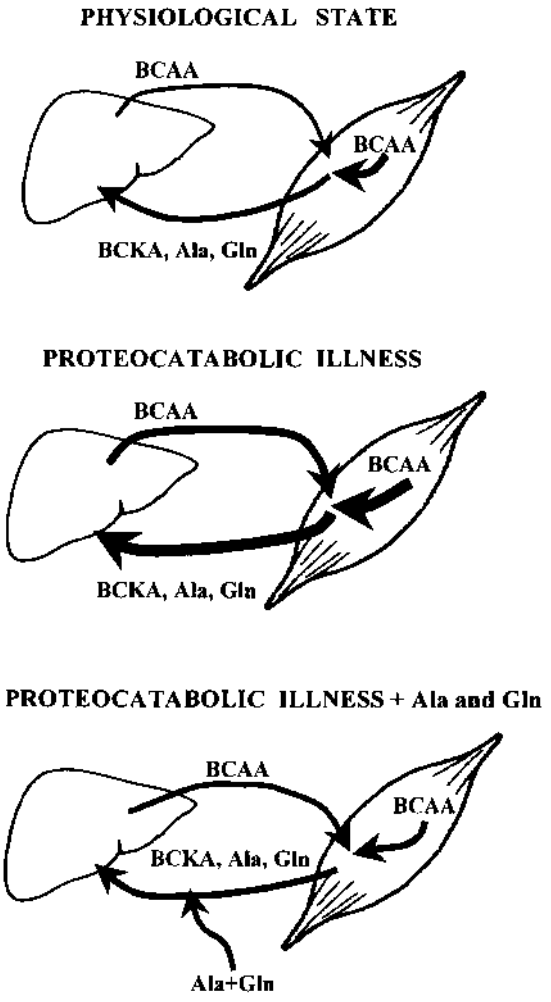

FIG. 3. The cooperation in the metabolism of BCAA, Ala, and Gln in the physiologic state, proteocatabolic illness, and proteocatabolic illness affected by administration of Ala and Gln. Ala, alanine; BCAA, branched-chain amino acid; BCKA, branched-chain keto acid; Gln, glutamine.

CONCLUSIONS

It is well established that that there is a cycle that enables resynthesis of BCAA from BCKA (Fig. 3, top) and that the turnovers of BCAA, glutamine, and alanine are markedly increased in conditions associated with muscle wasting such as in sepsis, cancer cachexia, burn injury, and trauma (Fig. 3, middle). As a result of activated protein breakdown, BCAAs are released from body proteins and extensively catabolized. The amino group released during transaminase reaction is used primarily for synthesis of alanine and glutamine. The increased protein breakdown and activated catabolism of BCAA enable the body to provide for its increased need for glutamine and alanine. Thus, the undesirable result of activated synthesis of alanine and glutamine in severe illness is protein wasting.

Observations of the effects of exogenous administration of glutamine (Ala-Gln) and activated synthesis of glutamine on BCAA and protein metabolism clearly demonstrate that the increase in glutamine concentration in body fluids markedly decreases whole-body protein breakdown (Fig. 3, bottom). These results might explain the mechanism of the favorable effect of exogenous glutamine (Ala-Gln) on protein metabolism.

A possible cause of the decreased rate of protein synthesis after glutamine or alanine infusion[27,28] is probably decreased amino acid availability resulting from decreased protein breakdown. Hence, the provision of alanine and glutamine together with sufficient amounts of other amino acids should significantly modify the effect of alanine and glutamine on protein turnover, in particular protein synthesis. The stimulatory effect of the amino acid solution enriched with glutamine on protein synthesis has been found in several studies.[8]

In conclusion, intervention in the pathway of the BCAA–BCKA cycle and its relation to the synthesis of alanine and glutamine might be a useful method of affecting the development of negative protein balance in severe illness. Some favorable effects of BCAA supply can be explained by their role in the synthesis of glutamine; conversely, some positive effects of glutamine exogenous supply can be explained by its effect on the metabolism of BCAA.

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