The Metabolic Role of Branched-Chain Amino Acids

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The liver is considered the major site of amino acid degradation.[1] However, skeletal muscles are another important site for amino acid metabolism because they catabolize branched-chain amino acids (BCAAs), which are unique. In addition to serving as a non-specific source of carbon for oxidation as fuel for the muscle, they serve as precursors for protein synthesis in the muscle. Experiments in the rat by Miller and Holden[2] suggested that substantial oxidation of leucine, isoleucine, and valine takes place extrahepatically. Manchester,[3] in a pioneering short communication published in 1965, provided a quantitative estimate of the capacity of the rat diaphragm to convert [^{14}C] amino acids into $^{14}CO_2$. Manchester's results showed that over half of the [^{14}C] leucine entering the tissue is decarboxylated in the diaphragm and that a considerable proportion is degraded even further. The percentages of decarboxylation for isoleucine (58%) and valine (31%) also were substantial. Addition of insulin brought about a small but consistent stimulation of leucine oxidation. Moreover, the fraction of isotope taken up by the diaphragm appearing as $^{14}CO_2$ did not decline markedly as the concentration of amino acids supplied rose, in contrast with the amount of isotope incorporated into protein, which dropped steadily as the specific activity fell.[3]

Further extensive work exploring the possibility that oxidation might be a major metabolic pathway for leucine (and possibly all three BCAAs) in rat diaphragm and in soleus and extensor digitorm longus muscles was published in 1972 by Odessey and Goldberg.[4] They determined that the diaphragm posseses a marked ability to degrade leucine -1-^{14}C to $^{14}CO_2$. The metabolism of leucine by the diaphragm depended on the concentration, and leucine uptake and oxidation increased with increasing external concentrations. Further, the amount of leucine degradation relative to its incorporation into protein increased 10-fold as its external concentration was raised. The red soleus and pale extensor degitorum longus muscles exhibited a similar marked capacity for leucine oxidation. The rates of CO_2 production, incorporation into protein, and total uptake in these two muscles were lower than those in the diaphragm.

The skeletal muscle mass, which constitutes 43% of the body mass, is the major site for leucine oxidation in the body, marking leucine and possibly the other BCAAs as significant energy sources for the muscle. Complete oxidation of leucine in the muscle yields more adenosine triphosphate molecules on a molar basis than complete oxidation of glucose. Further, this inherent ability of muscle to oxidize leucine increases under certain physiologic states such as food deprivation.[5] Later work determined that the rate of oxidation of BCAA in muscle is under metabolic and hormonal regulation. Buse and Reid[6] in skeletal muscle and Chua et al.[7] in cardiac muscle suggested that leucine also regulates the turnover of protein in muscle cells by inhibiting protein degradation and enhancing protein synthesis. This regulation of muscle protein turnover by leucine influences the transition to negative nitrogen balance during fasting, uncontrolled diabetes, and the posttraumatic state. Very recent studies have suggested that leucine activates a signaling pathway that enhances activity and synthesis of proteins involved in messenger RNA translocation to upregulate protein synthesis in skeletal muscle.

These and other extensive basic researches on the metabolism of BCAAs in general and leucine in particular have led to a worldwide interest in their possible use for metabolic support.

The possible clinical metabolic advantages of BCAAs for skeletal muscle were first examined in the nutrition support of patients with hepatic failure and encephalopathy. It was speculated that, beyond the competition of BCAAs with the aromatic amino acids at the blood–brain barrier, BCAA might exert other beneficial metabolic effects such as reducing the hypermetabolism and muscle catabolism inherent in liver failure and encephalopathy, supplying an alternative energy source, decreasing muscle proteolysis, and increasing muscle protein synthesis. Controlled, randomized, prospective studies with BCAA-enriched parenteral solutions in patients with cirrhosis and encephalopathy improved wake-up time, survival, and even nitrogen equilibrium in this group of highly catabolic patients.[8,9]

After the development and clinical use of a BCAA-enriched formulation for liver patients, the use of BCAA in injury and sepsis was investigated. Injury and sepsis are characterized by the activation of the pituitary–adrenal axis and the autonomic nervous system and by monokine production resulting in the altered metabolism of protein, carbohydrate, and lipids. This metabolic response to injury and sepsis produces a state of hypermetabolism and catabolism requiring optimal metabolic support. There are several possible benefits for the use of BCAA in these conditions: the skeletal muscle consumes its own BCAAs as part of the inherent catabolism of injury or sepsis, thereby depleting the muscle's own energy source; BCAAs can be converted to other fuels such as ketones or glutamine; and BCAAs stimulate muscle protein synthesis and decrease proteolysis.

Infusion of balanced amino acid formulations enriched with BCAA or even infusion of only the three BCAAs in experimental animals resulted in nitrogen equilibrium in a rat injury model and the normalization of injury-induced deranged plasma and muscle amino acid patterns. Infusing each BCAA separately decreased the total body protein breakdown rate.[10]

Clinical studies in injury or sepsis patients have shown the following beneficial effects of BCAA only or balanced BCAA-enriched parenteral nutrition solutions:

1. improved nitrogen retention and balance
2. stimulation of protein synthesis
3. improved visceral protein status
4. improved immune function parameters
5. normalization of plasma amino acid profile

Disappointingly, none of these beneficial effects of BCAA have demonstrated any significant change in injury or sepsis associated morbidity and mortality.[11]

The final answer to the question of the role of BCAA in the metabolic support of injured and septic patients remains to be established.

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REFERENCES

1. Bollman JL, Mann FC, Magath TB. Studies on the physiology of the liver: effects of total removal of the liver on deaminization. Am J Physiol 1926;78:258
2. Miller LL, Holden JT. The role of the liver and the non-hepatic tissues in the regulation of free anino acid levels in the blood. In: Holden JT, ed. *Amino acid pools.* Amsterdam: Elsevier, 1962:708
3. Manchester KL. Oxidation of amino acids by isolated rat diaphragm and the influence of insulin. Biochim Biophys Acta 1965;100:295
4. Odessey R, Goldberg AL. Oxidation of leucine by rat skeletal muscle. Am J Physiol 1972;223:1376
5. Goldberg AL, Odessey R. Oxidation of amino acids by diaphrams from fed and fasted rats. Am J Physiol 1972;223:1384
6. Buse M, Reid S. Leucine, a possible regulator of protein turnover in muscle. J Clin Invest 1975;56:1250
7. Chua B, Siehl D, Morgan H. A role for leucine in regulation of protein turnover in working rat hearts. Am J Physiol 1980;239:E510
8. Naylor CD, O'Rourke K, Detsky AS, Baker JP. Parenteral nutrition with BCAA in hepatic encephalopathy: a metanalysis. Gastroenterology 1989;97:1033
9. Cerra FB, Cheung NK, Fischer JF, et al. Disease specific amino acid solution in hepatic encephalopathy. JPEN 1985;9:288
10. Freund HR. Nutritional support of the trauma patien. In: Shackford SR, Perel A, eds. *Problems in critical care.* Philadelphia: JB Lippincott, 1987:651
11. Cerra FB, Mazuski JE, Chute E, et al. Branched chain metabolic support. A prospective, randomized, double-blind trial in surgical stress. Ann Surg 1984; 199:286