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

Application of Branched-Chain Amino Acids in Human Pathological States: Discussion of Session 4¹,²

John D. Fernstrom³

Departments of Psychiatry and Pharmacology and UPMC Weight Management Center,
University of Pittsburgh School of Medicine, Pittsburg, PA

Dr. Fernstrom started the discussion by asking Dr. Charlton, with regard to the Marchesini study he discussed, if this new study included measures beyond the simple outcome measures followed in the earlier study? If so, did the new measures provide some indication of the underlying biochemical or metabolic actions of the BCAA that might begin to explain some of the positive results? Dr. Charlton responded that they had tracked the components of the Child-Pugh-Turcotte score, which included albumin, bilirubin, and prothrombin time. These variables improved, and probably reflected increased liver hepatocyte mass, which was most likely the primary basis for the observed improvement. He added that after liver, muscle is the most important ammonia-producing organ and that at present an effect on muscle could not be excluded. Dr. Fernstrom then asked if the current view regarding the development of encephalopathy is that ammonia buildup is more important than elevated tryptophan uptake into brain. Dr. Charlton commented that he thought ammonia is important, though clearly not the whole story. Other transmitters, such as endogenous benzodiazepines and glutamate, appear to play a role; the etiology of encephalopathy is a multifactorial process.

Nevertheless, fluctuations in ammonia are reasonably predictive, and thus useful.

A question was then raised to Dr. Layman if, in his studies, all the symptoms of the metabolic syndrome could be reversed by the consumption of the high-protein diet. For example, what were the effects on high-density lipoproteins and triglycerides? Dr. Layman responded that all symptoms were reversed. He noted that when he compared the higher protein–lower carbohydrate and the lower protein–higher carbohydrate diets, the former produced a 25–30% drop in triglycerides compared with the latter diet, and always produced a small increase in the high-density lipoproteins. The higher carbohydrate–lower protein diet always reduced high-density lipoproteins; this diet also produced a slight reduction in the LDL/total cholesterol ratio, compared with the higher protein–lower carbohydrate diet, but the effect was transient. He added that his group had recently completed a 16-mo study with 130 subjects, and found that by 12 mo, the 2 diets produce about the same effects on total cholesterol and LDL, along with parallel weight loss. But, the positive effects of the high-protein diet on serum triglycerides and HDL were still present. On consideration of the question as to whether the effects of the higher protein diet were related to branched-chain amino acids, he thought that probably they were not.

Dr. Baracos then asked the session speakers, in relation to their study populations, to identify the single feature of a patient most predictive of a positive outcome to branched-chain amino acid supplementation. The responses were 1) a preexisting low protein intake or poor nutritional status; 2) the degree of emaciation, or the biggest reduction in body mass; 3) poor tolerance to standard dietary proteins.

Dr. Cynober noted that most trauma patients had high muscle levels of the branched-chain amino acids. He thus wondered what the rationale might be for expecting a positive response to further elevations of plasma branched-chain amino acid levels in such subjects in response to amino acid supplements. Dr. Rennie responded that he did not think this issue had been carefully examined, a position with which Dr. De Bandt agreed. Another participant suggested that perhaps supplemental amino acids had a sparing effect on endogenous amino acid and protein pools, for example, by providing an alternative source of the amino acids needed for the proliferative response to an immune challenge.

Dr. Volpi shifted focus to another topic, asking about the leucine effect on muscle protein synthesis after 8 h of leucine infusion. She noted that Dr. Rennie had shown data indicating that the infusion of a mixture of amino acids induced muscle protein synthesis for 2–3 h, after which, despite continued infusion, protein synthesis returned to baseline. She therefore wondered if measuring protein synthesis only at 8 h, and observing no treatment effect, would allow one to conclude that none had occurred at an earlier timepoint. Dr. Nair added that the effects in muscle of administering insulin and amino acids on transcriptional and translation events, and probably for particular transcripts and proteins as well, are likely to have unique time profiles. He noted that at present, relatively little

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² Author Disclosure: No relationships to disclose.
³ To whom correspondence should be addressed. fernstromjd@upmc.edu.
information exists regarding such time profiles, particularly for individual transcripts or proteins, and that careful time studies of this sort would be very useful. Dr. Charlton then commented that he did not imagine that protein synthesis would continue indefinitely; presumably, there would be a limit to the need for whatever proteins were being synthesized. Moreover, in studies in which only amino acids were infused, other important substrates for protein synthesis could become limiting, and thereby diminish protein synthesis. He offered as an illustration liver resection patients, noting that the livers of hypophosphatemic patients do not regenerate.

Dr. Fernstrom then asked Dr. Cano about his statement that tyrosine is effectively an essential amino acid in patients with chronic renal failure, and that tyrosine levels are low. He wondered why tyrosine was considered “essential” in these patients, and why it was so low. He also asked that if tyrosine levels were low, what would be the effect on tissue tyrosine pools of adding more branched-chain amino acids, given competitive transport carriers shared by tyrosine and the branched-chain amino acids across some blood–tissue interfaces. Dr. Cano responded that tyrosine synthesis from phenylalanine was impaired in these patients in kidney and liver. He added that there are probably changes in the transport across the blood–brain barrier for many amino acids, notably tyrosine and the branched-chain amino acids. One consequence might be abnormal neurotransmitter synthesis (catecholamines are synthesized from tyrosine). Dr. Fernstrom then suggested that it might make sense, given this tyrosine vulnerability, to include adequate tyrosine in the amino acid solutions administered to these patients. Another participant offered the comment that in studies using stable isotopes, kidney and liver had been shown to make equivalent amounts of tyrosine from phenylalanine. However, the liver catabolized the tyrosine, whereas the kidney did not. Hence, in kidney failure, overall tyrosine production declines, but tyrosine metabolism does not, causing tyrosine levels to go down. The effect would then be exacerbated by administering a commercially-available amino acid mixture which has very low tyrosine levels (because its solubility is limited in aqueous solutions).

A participant then asked about the mechanism responsible for the development of the “catabolic state” in a number of pathological conditions (e.g., trauma, injury), as well as after surgery. Another participant noted that within seconds of making an abdominal incision (a type of trauma), cortisol, adrenergic, and glucagon responses occur which are partly responsible for promoting net protein breakdown and the mobilization of energy substrates. He added that many patients also become insulin resistant, which would indirectly promote a catabolic state. With infection, cytokine responses can lead to further protein breakdown. Another participant wondered if this protein catabolic response to injury might have evolved to serve a useful function. The view was put forth that under conditions of stress and injury, the muscle transforms from an organ of locomotion to an organ of amino acid storage and supply. Its role in the sick person is to serve as a huge amino acid repository. Hence, one sees a large efflux of amino acids from the hind quarter or the leg in stress and injury; the effect has been well documented. Presumably this response evolved over millions of years and has survival value, although it’s not clear what that value might be in the operating room. This line of discussion was continued by Dr. Cynober, who noted that with elective surgery, protein synthesis declines, whereas in burn and trauma patients, protein catabolism rises. He suggested that, given this difference, the underlying physiopathologic processes may be different and that, until they are understood, one cannot be confident of the usefulness of providing glutamine, branched-chain, or other amino acids to such patients. Regarding other metabolic and hormonal signals that occur in trauma, he also noted that a good example is tumor necrosis factor, which can stimulate glucose production in some conditions and inhibit it in others (e.g., end-stage of sepsis). The point was that additional studies are needed to expand the knowledge base regarding the metabolic responses that occur in pathophysiological states involving stress. Only then can amino acid supplements be rationally given. Finally, Dr. Volpi noted that with catastrophic injuries, such as those that occur following burns, some published data indicated that catecholamines may contribute to the catabolic response, because propranolol, a β-adrenergic receptor antagonist, elicits a muscle sparing effect in burned children. Another participant added that the comment regarding β-receptor antagonists cannot be generalized, because most such studies have been in burn patients, where the effect was observed at least 25 d postinjury. He noted that though the finding was intriguing, it could not be extrapolated to other contexts, such as the situation just after injury, where catecholamines are immediately released, but a rise in protein catabolism is not seen. In this situation, β-antagonists would presumably have little effect on muscle.