Effects of Branched Chain Amino-acid-enriched Total Parenteral Nutrition on Amino Acid Utilization in Rats Bearing Yoshida Sarcoma

Lisa E. Crosby, Bruce R. Bistrian, Pei-ra Ling, Nawfal W. Istfan, George L. Blackburn, and Stacy B. Hoffman

ABSTRACT

We have studied the ability of branched chain amino-acid enriched total parenteral nutrition solutions to improve nutritional status without stimulating tumor growth. Protein kinetics, nitrogen balance, tumor growth, and the relationship with the type, duration, site, size, or number of complications were given as the sole source of amino nitrogen after injury it were significantly higher in tumor animals receiving crystalline infusions, suggesting greater tumor protein breakdown with branched chain amino acid-enriched diet. During the last 4 h of feeding, the protein kinetic values were studied using a constant infusion of $[^{14}C]$tyrosine. Plasma tyrosine appearance, synthesis, and breakdown were unchanged by branched chain amino acid infusion. Percentage of tyrosine flux oxidized and tyrosine oxidation decreased ($P < 0.05$) and net tyrosine balance improved ($P < 0.05$) in rats receiving the branched chain amino acid-enriched diet. Greater nitrogen balance and lower tumor growth rates were also found in branched chain amino acid-infused rats although not statistically significant. Tumor intracellular specific activity was significantly higher in tumor animals receiving crystalline infusions, suggesting greater tumor protein breakdown with branched chain amino acid-enriched infusion. Fractional synthetic rates of liver, muscle, and tumor were unchanged. Hence, branched chain amino acid-enriched total parenteral nutrition increases amino acid utilization for net protein synthesis principally by reducing oxidation without stimulating tumor growth.

INTRODUCTION

Cancer cachexia is recognized as a primary cause of death in many types of cancer (1). In fact, protein malnutrition is the single most common secondary diagnosis in cancer patients (2). Failure to prevent protein malnutrition increases the risk of developing complications, aggravates antineoplastic therapy, reduces the quality of life, and increases morbidity and mortality (2–5).

Although malnutrition may result from interference with gastrointestinal function, the usual cachexic syndrome developing in the course of malignant disease often cannot be explained by depression of food intake due to local factors alone and behaves as if it were the result of a systemic alteration including anorexia induced by the tumor (6). Furthermore, the weight loss accompanying cancer in humans bears no consistent relationship with the type, duration, site, size, or number of metastases (7).

Recent evidence indicates a similarity between the metabolic response to injury and active tumor growth (8). This similarity raises interest in a possible role for BCAA in modifying the metabolic response of the tumor-bearing host. When BCAA were given as the sole source of amino nitrogen after injury it reduced the loss of body protein by 15–80% in rats (9–12) and man (13, 14). In vitro, BCAA inhibit protein degradation and promote protein synthesis (15) and have specific regulatory functions in the turnover of skeletal muscle protein (16). Hence, the regulatory effect of BCAA on muscle protein turnover needs to be further characterized in relationship to host tissues as well as the tumor itself.

Studies by Schaur and his associates demonstrated that continuous p.o. administration of BCAA to rats bearing Yoshida sarcoma significantly increased survival time by 32% and reduced tumor size by 33% after 3 wk of growth (17). Their work also demonstrated that a shift in nitrogen balances was delayed, but not prevented, by BCAA administration (17). In our laboratory, Kawamura et al. found that BCAA-enriched solutions infused into animals bearing RNC-fibrosarcoma limited the reduction in skeletal protein synthesis seen in tumor-bearing animals receiving standard amino acid formulas (18). Also, Tayek and his coworkers gave parenteral infusions containing 50% BCAA-enriched solutions to malnourished patients with intraabdominal metastatic adenocarcinoma and improved whole body leucine flux, oxidation, leucine balance, and fractional synthetic rates of albumin (19). However, there was concern in the latter study that the choice of leucine as the tracer when leucine-enriched solutions are studied might lead to underestimates of leucine oxidation and therefore overestimates of leucine balance. Thus, we sought to confirm the benefits of parenterally administered BCAA for kinetic estimates of protein metabolism using tyrosine as the amino acid tracer. Since the tyrosine content of both formulas is very low and lower in the BCAA-enriched solution, a finding of improvement in parameters of protein metabolism with the BCAA-enriched solution using tyrosine as the tracer amino acid in a second animal tumor model would lend further support to their potential value for nutritional repletion in cancer cachexia.

MATERIALS AND METHODS

Animal Preparation and Nutrient Infusion. Thirty-three specific pathogen-free male Sprague-Dawley rats (35–40 g) were obtained from Taconic Farms (Germantown, NY). The study was conducted under the approval of the Animal Care Committee at the New England Deaconess Hospital and in compliance with their established rules and guidelines. Prior to the experiment, rats were housed, for a minimum of 5 days, 2 to a cage and maintained on a 12/12 h light/dark photoperiod at an ambient temperature of 27 ± 1°C. Tap water and rodent chow (Charles River D-3000; Agway Agricultural Products, Minneapolis, MN) were provided ad libitum.

The Yoshida sarcoma tumor cell line was used to induce cancer cachexia. The study was conducted from day 10 to 14 which is on the linear portion of the tumor growth curve and was determined to be a cachectic period (Fig. 1). On day 0 of the study, 15 animals were inoculated with $10^6$ cells of viable Yoshida sarcoma into the s.c. area of the right flank. The non-tumor-bearing rats were given an identical sham injection with sterile saline. The animals were weighed, returned to their cages, and allowed to consume standard laboratory chow and tap water ad libitum. The animals were not pair fed and the rats bearing rapidly growing tumors had diminished food intake, reflecting the presence of tumor. On day 10, the tumor-bearing animals weighed less.
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Fig. 1. Weight gain of tumor-bearing and control rats. The Yoshida sarcoma tumor cell line was used. Tumors were palpable by day 5 in all animals. Tumor growth followed first order kinetics and the study was conducted from day 10 to 14 which was previously determined to be the cachetic period. • control; +, Yoshida sarcoma.

Table 1 Dietary intake

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Control group</td>
<td>45.6</td>
<td>174.4</td>
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</tr>
<tr>
<td>Test group</td>
<td>51.6</td>
<td>168.4</td>
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<tr>
<td>Diets with one half dextrose calories</td>
<td>Dextrose = 10.7%</td>
<td>Dextrose = 10.0%</td>
<td>Dextrose = 21.4%</td>
<td>Dextrose = 20.9%</td>
</tr>
<tr>
<td>Regular diet</td>
<td>Amino acid = 3.7%</td>
<td>Amino acid = 4.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Branched chain enriched diet</td>
<td>Amino acid = 3.7%</td>
<td>Dextrose = 10.7%</td>
<td>Dextrose = 10.4%</td>
<td>Dextrose = 10.0%</td>
</tr>
<tr>
<td>Diets with full dextrose calories</td>
<td>Dextrose = 21.4%</td>
<td>Dextrose = 21.4%</td>
<td>Dextrose = 20.9%</td>
<td>Dextrose = 20.9%</td>
</tr>
<tr>
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<td>Amino acid = 3.7%</td>
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<tr>
<td>Branched chain enriched diet</td>
<td>Amino acid = 3.7%</td>
<td>Dextrose = 21.4%</td>
<td>Dextrose = 21.4%</td>
<td>Dextrose = 21.4%</td>
</tr>
<tr>
<td>Additive per 1500 ml</td>
<td>NaCl 45 mEq</td>
<td>NaAc 45 mEq</td>
<td>KCl 45 mEq</td>
<td>KAc 37 mEq</td>
</tr>
</tbody>
</table>

Table 1 Dietary intake (kcal/kg/body weight) which has been demonstrated to be a sufficient time to reveal differences if they indeed exist. Hyperalimentation in a small tumor-bearing rat for a longer period of time (i.e., 10-14 days) is difficult to accomplish due to technical failures and an increase in mortality. Twenty four-h urine was collected for nitrogen balance determination.

Isotopic Turnover Design. On day 14, [14C]tyrosine (350 mCi/mmol; ICN, Irvine, CA) was added to the diets and a 4-h constant infusion was conducted to investigate protein kinetics. Each animal received 1.7 µCi/h of [14C]tyrosine at a volume rate of 1.67 ml/h through a syringe pump (±1%; Harvard Apparatus Co., S. Natick, MA). Total carbon dioxide production, O2 consumption, respiratory quotient, and resting energy expenditure were determined during the infusion as previously described (20). VO2 and VCO2 were measured by methods previously published by our laboratory (20).

At the end of the infusion, the animals were sacrificed by decapitation and the blood was collected in heparinized tubes. Plasma was separated by centrifugation and stored at −25°C. Immediately following decapitation, the body was quickly dissected, and the liver, tumor, and portions of the abdomen rectus muscle were removed. The liver was weighed and 1-g pieces were placed in 5 ml of 10% sulfosalicylic acid and 5 ml of saline and then completely frozen in liquid nitrogen (−180°C) to halt all metabolic processes. Two 1-g pieces of muscle were similarly frozen. The tumor was weighed and also frozen intact in liquid nitrogen. All samples were stored at −25°C until analysis. The total time between decapitation and sample freezing in liquid nitrogen was 2–3 min.

Analytical Methods. VO2, VCO2, respiratory quotient, and resting energy expenditure were derived from the equations of Weil (21). Total urinary nitrogen was determined following a micro-Kjeldahl digestion.

In preparation for the tyrosine and albumin specific activity assays, the plasma was thawed and deproteinized with 10% trichloroacetic acid (2:1 v/v; plasma:trichloroacetic acid). Following centrifugation, the supernatant was analyzed for free tyrosine specific activity as previously described (22). Tyramine concentration was determined by the method of Waksleek and Underfend (23).

The protein pellet was analyzed for albumin specific activity by means of an ethanol-water extraction. One ml of the extracted supernatant was added to 10 ml of commercial scintillant (Monokomhu; National Diagnostics, Manville, NJ) with 100 µl of glacial acetic acid to supress chemiluminescence and analyzed, in duplicate, for 14C radioactivity (LS-8000 spectrometer; Beckman, Fullerton, CA). To determine albumin concentration, 25 µl of the ethanol supernatant were transferred, in duplicate, into test tubes containing 6 ml of a bromocresol green solution (General Diagnostics, Morris Plains, NJ) and distilled water (1:5 v/v solution) and vortexed for 10 sec. The samples were analyzed spectrophotometrically at a wavelength of 630 nm. Albumin concentrations were determined by linear regression of known standards, and unknowns were determined from the regression line.

The tissue samples, liver, abdomen rectus muscle, and tumor were thawed and homogenized (Polytron; Brinkmann Instruments, Westbury, NY). Nitrogen content of tissue samples stored in saline was determined by micro-Kjeldahl digestion. Homogenized tissue samples stored in sulfosalicylic acid were centrifuged at 4500 rpm to separate the acid-soluble amino acids (Si) from protein-bound precipitate (Sb). The acid-soluble amino acid supernatant for each sample was analyzed for tyrosine specific activity as stated previously. The protein-bound precipitate was washed with sulfosalicylic acid and reprecipitated. The protein pellet was then dried at 100°C.

To determine the amount of tyrosine in the protein-bound precipitate, 200-µg samples of wet tissue (liver, muscle, and tumor) were obtained from noninfused animals. These samples were hydrolyzed in 10 ml of 6 N HCl at 115°C for 24 h. Tyrosine concentration (µmol tyrosine/mg protein) of the hydrolysate was determined on a reverse-phase column (C18 Bondapack; Waters Associates, Milford, MA) by high performance liquid chromatography using gradient elution with phosphate buffer and 65% methanol and precolumn derivitization with o-phthalaldialdehyde and fluorescence detection. Nitrogen content (N/g) of 40 mg of dried protein-bound precipitate was determined by micro-Kjeldahl digestion. Two ml of Tissue Solubilizer-450 (Beckman Instruments, Inc., Fullerton, CA) were added to another 40-µg aliquot of the non-tumor-bearing animals, indicating their cachectic state. The rats were anesthetized with ether and a Silastic catheter (0.025 inside diameter x 0.047 in outside diameter; Dow-Corning Laboratories, Comining, NY) was inserted into the internal jugular vein as previously described (20). The animals were placed in metabolic units and anesthetized with ether and a Silastic catheter (0.025 inside diameter x 0.047 in outside diameter; Dow-Corning Laboratories, Comining, NY) was inserted into the internal jugular vein as previously described (20). The animals were placed in metabolic units and anesthetized with ether and a Silastic catheter (0.025 inside diameter x 0.047 in outside diameter; Dow-Corning Laboratories, Comining, NY) was inserted into the internal jugular vein as previously described (20).
dried protein-bound precipitate and the samples were incubated overnight at 50°C. Ten ml of commercial scintillant (Beckman NA) were added to the vials with 200 µl of glacial acetic acid to suppress chemiluminescence and analyzed for 14C radioactivity (dpm/mg) (Beckman LS-8000 spectrometer).

Rate of whole-body tyrosine appearance, oxidation, percentage of tyrosine oxidized, synthesis, breakdown, and tyrosine balance were estimated from the equations of Waterlow (24). It was assumed that a plateau labeling (steady state) of the plasma compartment was achieved when the S* was reached in the expired breath (between 2 to 3 h of continuous [14C]tyrosine infusion) (25). Plasma tyrosine appearance can be attributed to the degradation of body protein, dietary intake, or hydroxylation of phenylalanine (Fig. 1). It was previously shown in our laboratory that approximately 22% of tyrosine flux is derived from phenylalanine (26). Studies done by other investigators (27) have shown similar proportions of phenylalanine-derived plasma tyrosine, suggesting that this fraction is relatively stable in animals with normal liver function. In this experiment, most of the plasma phenylalanine flux is derived from protein breakdown since dietary intake was negligible (Table 1). Under these conditions, it can be shown that a 50% increase in the rate of conversion to tyrosine will result in only a 10% increase in tyrosine appearance in excess of what is derived from breakdown. Therefore, it is appropriate to consider that changes in plasma tyrosine appearance in this study are closely related to changes in whole-body protein breakdown. The protein fractional synthetic rates in the liver, abdominal rectus muscle, and tumor were derived from the equations of Garlick et al. (28).

Estimates of fractional tumor growth, Kp, were derived from tumor volume measurements on days 10 and 14. Tumor volumes were estimated from measurements of tumor length, width, and depth in millimeters as previously described (29). These measurements bear a close relationship to tumor weight. Tumor protein breakdown rates were estimated as the difference between tumor protein synthesis, measured isotopically, and tumor growth.

Statistical Analysis. Data are presented as mean ± SEM. The data from groups one through four were compared for statistical differences using two-way and one-way analysis of variance using statistical software (BMDP Statistical Software, Los Angeles, CA).

RESULTS

During a constant infusion of L-[U-14C]tyrosine, radioisotope excretion in expired breath generally reached a steady state within 2–4 h. Whole-body tyrosine kinetic values are shown in Table 2. There was no significant difference in mean whole-body protein flux due to BCAA infusion. The use of BCAA-enriched diets significantly reduced whole-body tyrosine oxidation and percentage of flux oxidized compared to animals given a standard formula containing 19% BCAA in both tumor and non-tumor-bearing animals. Although tyrosine incorporation into protein and release by tissue breakdown were not statistically different between the two groups, tyrosine balance was improved (P < 0.05) by BCAA administration in both tumor and non-tumor-bearing animals. The greater sensitivity of tyrosine balance to detect differences over the individual components incorporation and breakdown has been previously noted (30). The effectiveness of BCAA in non-tumor-bearing animals may be attributable to the presence of a stress response related to the catheterization.

Nitrogen analysis revealed significantly higher nitrogen balance in tumor-bearing rats versus the nontumor controls (Fig. 2). The greater nitrogen retention in the tumor-bearing animals may be due to the tumor functioning as a "nitrogen trap" (29) particularly as the animals were studied during a rapid tumor growth phase. Also, the nitrogen balance of both the tumor and non-tumor-bearing animals infused with BCAA-enriched solutions was numerically higher than those infused with crystalline solutions.

All of the animals in the study lost weight, but there were no significant differences in final body weight or weight change. The weight loss may be explained by the small size of the animals, the effects of surgical stress, and the administration of only half of the dextrose calories the first night of feeding to allow for adaptation to parenteral glucose.

Tumor measurements and kinetics are displayed in Table 3. There were no significant differences in tumor volume, weight, percentage of body weight, or fractional synthetic rates due to diet manipulation. The growth rate of the Yoshida sarcoma, as indicated by measurements of tumor volume, was decreased to an insignificant degree by BCAA infusion. Tumor breakdown rates, determined by the difference between tumor synthesis and tumor growth, were higher but also not significant in the animals receiving BCAA-enriched infusions. Of note, however, tumor intracellular specific activity was significantly higher (P < 0.05) in animals infused with crystalline amino acids which is consistent with greater tumor breakdown with BCAA infusion.

The rates of fractional protein synthesis were calculated using the specific radioactivities of the plasma and the protein bound precipitate. No change in the synthetic rates of liver, rectus

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Nontumor</th>
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<tbody>
<tr>
<td>BCAA (7)</td>
<td>Crystalline amino acids (8)</td>
</tr>
<tr>
<td>Flux</td>
<td>42.1 ± 4.9</td>
</tr>
<tr>
<td>% of flux oxidized</td>
<td>14.4 ± 2.5</td>
</tr>
<tr>
<td>Oxidation</td>
<td>5.7 ± 0.8</td>
</tr>
<tr>
<td>Synthesis</td>
<td>36.4 ± 4.8</td>
</tr>
<tr>
<td>Breakdown</td>
<td>40.0 ± 4.8</td>
</tr>
<tr>
<td>Tyrosine balance</td>
<td>−3.6 ± 0.8</td>
</tr>
</tbody>
</table>

* Mean ± SEM (µmol/h/g body weight). ** P < 0.05 two-way analysis of variance (BCAA versus CAA).

Fig. 2. Nitrogen balance. Nitrogen balance was determined to be significantly higher in tumor-bearing animals as compared to non-tumor-bearing animals. The animals infused with BCAA-enriched solutions were in a more positive state than those infused with crystalline solutions, but this did not reach a level of statistical significance. Mean ± SEM, P < 0.05 tumor versus nontumor.
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There were no significant differences in tumor volume, weight, percentage as body weight, or fractional synthetic rate due to diet manipulation. Growth rate as indicated by measurements of tumor volume was decreased, but not at a significant level. Tumor protein breakdown rates (fractional synthetic rate — growth rate) increased in rats infused with BCAA-enriched diets, but not significantly. Intracellular specific activity (normalized for total infusate volume) was significantly lower in rats receiving BCAA suggesting greater tumor protein breakdown with BCAA-enriched infusions.

<table>
<thead>
<tr>
<th>Tumor BCAA</th>
<th>Tumor crystal-line amino acids</th>
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</thead>
<tbody>
<tr>
<td>Tumor volume, day 10 (mm³)</td>
<td>5336 ± 3990</td>
</tr>
<tr>
<td>Tumor volume, day 14 (mm³)</td>
<td>7202 ± 3874</td>
</tr>
<tr>
<td>Tumor weight, day 14 (g)</td>
<td>6.9 ± 4.9</td>
</tr>
<tr>
<td>Tumor weight/body weight, day 14 (%)</td>
<td>4.3 ± 3.3</td>
</tr>
<tr>
<td>Tumor fractional synthetic rate (%/day)</td>
<td>21 ± 6</td>
</tr>
<tr>
<td>Tumor growth rate (%/day)</td>
<td>5.1 ± 5.4</td>
</tr>
<tr>
<td>Tumor protein breakdown rate (%/day)</td>
<td>16 ± 7</td>
</tr>
</tbody>
</table>
| Intracellular specific activity (dpm/μmol/mI infusate) | 1204 ± 151 | 1967 ± 268*

* P < 0.05.

DISCUSSION

Cancer-associated cachexia is the primary cause or an associated phenomenon in many tumor-related deaths (1). Early experience suggested that poor nutrition in cancer patients interfered with therapy similar to the situation found in acute or chronic nonmalignant illness, and that malnutrition could interfere with the delivery of the optimal oncological therapy (31). Moreover, other evidence had been gathered that nutritional repletion of the malnourished cancer patient with standard regimens was difficult, if not impossible (32). In considering the consequences of protein malnutrition in the tumor-bearing host, we sought to develop a more effective nutritional support therapy through the use of BCAA.

In patients with actively growing neoplasms, plasma amino acid profiles are characterized by reduced BCAA levels and arterial-venous differences across skeletal muscle reflect an increased proportion of BCAA being oxidized (33). BCAA administered p.o. were shown to increase survival time and nitrogen balance while reducing tumor growth (17). There is also evidence for a beneficial effect of BCAA-enriched infusion on plasma leucine and albumin kinetics in humans (19) and muscle protein turnover in animals with cancer (18).

This study examined the effects of BCAA on host protein synthesis, breakdown, and growth. Although tyrosine is not an essential amino acid and rates of tyrosine release from protein breakdown cannot be derived from its appearance without additional assumptions, the rate of tyrosine oxidation and incorporation into protein can be evaluated (34). There was a significant reduction in whole-body tyrosine oxidation and percentage of tyrosine flux oxidized in the animals given BCAA infusions. Also, with the reasonable assumption that tyrosine appearance by de novo synthesis from phenylalanine does not differ between the two diet groups, net tyrosine balance was significantly greater in animals infused with BCAA-enriched solutions. Even without this assumption, the de novo synthesis of tyrosine is very small in relation to tyrosine appearance from breakdown and is unlikely to seriously affect the tyrosine balance calculation.

In injury and sepsis, the metabolic response is characterized by the net degradation of muscle protein and the mobilization of body fat for energy substrates and gluconeogenesis (35). BCAA are preferentially utilized in skeletal muscle and it has been hypothesized that BCAA supplementation may provide a protein-sparing metabolic fuel when energy demands increase due to the metabolic response to stress or disease. Freud et al. hypothesized that BCAA spared nitrogen by providing substrates for muscle fuel catabolism, by providing amino groups to produce alanine for hepatic gluconeogenesis, and by blocking amino acid efflux from muscle (36). Although the metabolic response in a tumor model is somewhat different from an injury or trauma model, there are numerous similarities (8) and these principles of BCAA utilization may apply in the tumor-bearing host. Administration of TPN solutions enriched with BCAA reduces whole-body tyrosine oxidation and percentage of tyrosine flux oxidized and spares body protein by improving amino acid reutilization through nonoxidative pathways. Thus, such a dietary intervention may favorably influence net protein metabolism in the carcass without enhancing tumor growth.

The tumor-bearing animals retained more nitrogen than the non-tumor-bearing animals (P < 0.05). This significant difference may be due to the tumor functioning as a nitrogen trap where tumor breakdown is minimal, limiting systemic reentry of amino acids.

Tumor volume, weight, and percentage of body weight indicate a rapidly growing sarcoma. In the clinical setting, tumors grow at slower rates and rarely comprise more than 1% of total body weight when patients die from metastatic disease. The work of Tayek et al. with the Walker 256 carcinosarcoma demonstrated variable tumor growth rates of the same tumor type in different animals and postulated that accelerated tumor growth was related more to reduction of tumor protein breakdown rates than to stimulation of tumor protein synthesis (29). Tumor protein breakdown rates were numerically higher in animals receiving BCAA-enriched infusions which is consistent with the significant reduction in tumor intracellular specific activity in animals receiving branched chain amino acid-enriched diets. The slightly lower tyrosine content in the BCAA-enriched diet would increase the specific activity of the infusate, rather than lowering tumor intracellular specific activities, as seen in our study, thus lending support to our hypothesis that BCAA-enriched infusions increase tumor protein breakdown.
Thus, the data suggest that administration of TPN solutions enriched with BCAA does not stimulate tumor growth but does support host protein metabolism and may play a role in retarding tumor growth by increasing tumor protein breakdown rates.

In conclusion, our results suggest that BCAA-enriched TPN solutions increase amino acid utilization for net protein synthesis by the host principally by reducing oxidation without stimulating tumor growth. The site of the improved protein balance was not specifically identified but presumably was in skeletal muscle due to the large size of this component as well as being the usual major site of net nitrogen balance during feeding. Such a location would also be consistent with the mode of action of BCAA to reduce net skeletal protein catabolism. These observations may be important for the development of optimal nutritional support therapies for cancer patients in the treatment of cancer cachexia. Improved support regimens might afford a heretofore undetected benefit of nutritional support in randomized trials of cancer patients receiving chemotherapy (37) and might also be an effective means to slow the progression of the cachexia syndrome and prolong life where effective chemotherapy does not exist. Finally, the suggestive effect of BCAA-enriched total parenteral nutrition to increase tumor growth by increasing tumor protein breakdown rates deserves further investigation over a longer study period.

REFERENCES

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