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Alanyl-Glutamine Dipeptide-Supplemented Parenteral Nutrition Improves Intestinal Metabolism and Prevents Increased Permeability in Rats

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Objective

The authors determined the effects of alanyl–glutamine-supplemented total parenteral nutrition (TPN) on mucosal metabolism, integrity, and permeability of the small intestine in rats.

Methods

Male Sprague-Dawley rats were randomized to receive TPN supplemented with a conventional amino acids mixture (STD group) or the same solution supplemented with alanyl-glutamine; both solutions were isocaloric and isonitrogenous. On the seventh day of TPN, D-xylose and fluorescein isothiocyanate (FITC)-dextran were administered orally. One hour later, superior mesenteric vein (SMV) D-xylose and plasma FITC-dextran concentration were measured. Intestinal blood flow and calculated intestinal substrates flux were measured with ultrasonic transit time flowmetery.

Results

Plasma FITC-dextran increased significantly in the STD group. Intestinal blood flow and SMV D-xylose concentration did not differ between the groups. Mucosal weight, villus height, mucosal wall thickness, mucosal protein, and DNA and RNA content in jejunal mucosa were significantly increased in the alanyl-glutamine group. Jejunal mucosal glutaminase activity and net intestinal uptake of glutamine (glutamine flux) were significantly higher in the alanyl-glutamine group as compared with the STD group.

Conclusion

Addition of alanyl-glutamine dipeptide to the TPN solution improves intestinal glutamine metabolism and prevents mucosal atrophy and deterioration of permeability.

Total parenteral nutrition (TPN)-induced changes in structure and enzyme activity of intestinal mucosa[1] are associated with increased permeability of the intestine,[2] and probably increase the risk of bacteremia and endotoxemia.[3] These changes may be attributed to the absence of amino acid glutamine in commercially available amino acid solutions because glutamine is known to be an important metabolic fuel of the enterocyte.[4–6] Glutamine is not included in conventional TPN solutions because it is unstable during storage. The availability of dipeptides, which are stable in solution and rapidly hydrolyzed after intravenous infusion, has made it possible to perform glutamine-supplemented TPN.[7–9] In experimental animal models, the addition of free glutamine and glutamine dipeptide to TPN solution demonstrated beneficial effects on intestinal morphology.[10,11] In this study, we report the effect of alanyl-glutamine dipeptide-enriched TPN on small intestinal mucosal metabolism, integrity, permeability, and absorptive capacity.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (n = 26; range, 230–240 g), obtained from Oriental Yeast Company, (Osaka, Japan) were used. Before the experiment, the experimental animals had free access to standard rat food (Oriental MF; Oriental Yeast Co., Osaka, Japan) and tap water while in their cages and were acclimatized to standard conditions in our laboratory, with approximately 40% to 60% humidity at room temperature of 23 C. The rats were subjected to alternate 12-hours periods of dark and light cycles.

Surgical Procedures and Nutrition

After an overnight fast, rats (n = 18) were anesthetized with intraperitoneal injection of sodium pentobarbital (30 mg/kg). The neck and interscapular region were shaved and prepared in a sterile manner for catheterization. A Silastic catheter (inner diameter, 0.25mm; outer diameter, 0.47 mm; Dow Corning, Midland, MI) was inserted through the right jugular vein. The catheter was tunneled subcutaneously and was brought out through the skin of the midscapular region. Rats were maintained in individual metabolic cages, and the nutrient solution was infused at a constant infusion rate by a pump. After catheterization (from day 0), rats were infused with normal saline for 24 hours. From the morning of the first postoperative day (day 1), rats were randomized to receive TPN supplemented with conventional amino acids mixture other than glutamine (STD group, n = 9) or the same solution supplemented with alanyl-glutamine 2 g/100 mL (alanyl-glutamine group, n = 9); both TPN solutions were isonitrogenous and isocaloric. The daily dose of amino acids infused was 2.5 g of nitrogen per kilogram, and the amount of nonprotein calories given was 250 kcal/kg per day as glucose. Multivitamins and electrolytes also were included in TPN solutions.

After 7 days of TPN, intestinal absorptive capacity and macromolecular permeability were tested in all rats. For this purpose, a solution of D-xylose 0.5g/kg body weight and FITC-dextran 750 mg/kg body weight were prepared in distilled water in a concentration of 50 mg of D-xylose and 75 mg of FITC-dextran per milliliter. This marker solution was given by gavage (1 mL/100 g body weight) under light ether anesthesia. After 1 hour, with the rats under intraperitoneal sodium pentobarbital anesthesia (30 mg/kg body weight), a midabdominal incision was made. One millimeter flow probe of ultrasonic transit time flow meter was positioned around the superior mesenteric vein (SMV) and kept in place for 2 minutes, followed by recording of blood flow signals for 1 minute. Immediately after recording SMV blood flow, blood samples were taken from the SMV and abdominal aorta (AA) as quickly as possible for the analysis of SMV D-xylose, plasma FITC-dextran, and whole blood glutamine and alanine concentration.

Immediately after sampling of blood from the SMV and AA, a considerable length of the small intestine from the ligament of Treitz was rapidly dissected free of its mesentry and flushed with ice-cold 0.9% saline. The intestine was suspended from its distal end while a 5.0-g weight was attached to the proximal end to enable accurate and reproducible demarcation of intestinal segments. The 3 cm of jejunum from the ligament of Treitz were discarded. The next 2 cm were used for histologic studies, and the next 20-cm segment of jejunum was used for measurement of mucosal wet weight, for analysis of mucosal protein content and mucosal DNA and RNA content, and for the determination of mucosal phosphate-dependent glutaminase activity.

Processing of Samples and Measurement

Plasma was separated from the blood samples by centrifugation and stored at −70 C until analysis. All samples were analyzed within 1 week. D-xylose concentration in the SMV blood was determined by colorimetric micromethod.[12] Quantification of FITC-dextran was performed by fluorescence spectrometry, as described by Westrom et al.[13] The measurement were made with a

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Table 1. JEJUNAL MORPHOLOGY AND MUCOSAL BIOCHEMISTRY

	Control Group (n = 8)	STD Group (n = 9)	Ala-Gln Group (n = 9)
Mucosal wet weight (mg/cm)	35 ± 4.5	11.5 ± 1.7*	19.9 ± 2.4*†
Villous height (μm)	513 ± 48	358 ± 32*	451 ± 38*†
Crypt depth (μm)	168 ± 82	145 ± 15	134 ± 19
Mucosal wall thickness (μm)	681 ± 120	503 ± 37*	585 ± 55*†
Mucosal protein (mg/cm)	2.7 ± 0.76	0.97 ± 0.13*	1.8 ± 0.34*†
Mucosal DNA (mg/cm)	0.22 ± 0.11	0.07 ± 0.01*‡	0.17 ± 0.1
Mucosal RNA (mg/cm)	0.24 ± 0.09	0.09 ± 0.01*	0.15 ± 0.03*†

STD = rats receiving total parenteral nutrition supplemented with conventional amino acid mixture; Ala-Gln = rats receiving alanyl-glutamine-supplemented total parenteral nutrition.
All values = mean ± standard deviation.
* $p < 0.05$ *vs.* control group.
† $p < 0.05$ *vs.* STD group.
‡ $p < 0.05$ *vs.* Ala-Gln group.

Hitachi fluorescence spectrophotometer (F-3000, Hitachi Ltd., Tokyo, Japan) at an excitation wavelength of 480 nm and an emission wavelength of 520 nm. Standard curves for calculating FITC-dextran concentration in the samples were obtained from dilutions of various FITC-dextrans in a pool of rat plasma. One hundred microliters of the standards or the plasma samples were diluted with 1.9 mL of 0.9% saline before measurement.

A fraction of blood samples of the SMV and AA were immediately deproteinized with equal volume of 2.5% sulfosalicylic acid to measure the whole blood glutamine and alanine concentration by an amino acid auto analyzer (Beckman amino acid analyzer System 7300, Beckman Instruments, Inc., Palo Alto, CA).

For biochemical analysis, the segment was opened longitudinally, and the mucosa was scraped immediately from the underlying muscular layer with a glass slide on an ice-cold surface. After the mucosa was weighed, it was homogenized in 10 volumes of extraction medium with a microhomogenizer at 0 to 4 C. The whole homogenate was used for protein measurement, DNA and RNA measurement and the phosphate-dependent glutaminase activity assay. Protein content was determined according to the method of Bradford,[14] and results were reported in milligrams per centimeter. DNA and RNA were measured by the method of Prasad et al.[15] and reported in milligrams per centimeter. Glutaminase activity was determined by the method of Curthoys and Lowry[16] and was expressed as micromoles per hour per milligram protein at 37 C.

For histologic evaluation of isolated jejunal segments, tissues were fixed in 10% volume/volume formalin, embedded in paraffin, and stained with hematoxylin and eosin. Three paraffin sections were prepared from each fixed tissue sample, and each slide was analyzed. Villus height, crypt depth, and mucosal wall thickness were determined on tissue cross-sections with an eyepiece micrometer with a magnification of 100 ×. Measurements were made in triplicate in a blind fashion on coded slides, and mean values were obtained. Eight normal, healthy rats raised on rat chow were killed, and samples were obtained to serve as controls.

Calculations

Absolute intestinal blood flow in each rat was obtained from the mean of the SMV blood flow signals, recorded for 1 minute. Blood flow was expressed as mL/100 g body weight/minute. Net intestinal uptake or release of substrates (substrate flux) was calculated by multiplying the AA–SMV concentration difference of each substrate by intestinal blood flow. Intestinal fractional uptake or release was calculated by using the formula ([AA concentration − SMV concentration]/AA concentration) and expressed as a percentage. Flux was expressed as nmol/100 g body weight/minute. A negative value indicated net release, whereas a positive value indicated net uptake.

Statistical Analysis

Data were represented as mean ± standard deviation. Analyses were performed among the three groups, using analysis of variance and Fisher's PLSD multiple comparison test. A p value of less than 0.05 was considered significant.

Table 2. INTESTINAL ABSORPTIVE CAPACITY AND PERMEABILITY

	SMV D-Xylose (mmol/L)	Plasma FITC-Dextran (μg/Ml)
Control group (n = 8)	0.72 ± 0.3	0.53 ± 0.6
STD group (n = 9)	0.95 ± 0.4	5.06 ± 4.7*†
Ala-Gln Group (n = 9)	1.05 ± 0.3	2.01 ± 1.5

STD = rats receiving total parenteral nutrition supplemented with conventional amino acid mixture; Ala-Gln = rats receiving alanyl-glutamine-supplemented total parenteral nutrition.
All values = mean ± standard deviation.
* $p <$ vs. 0.05 control group.
† $p <$ vs. 0.05 Ala-Gln group.

RESULTS

Jejunal Morphology and Mucosal Biochemistry (Table 1)

Mucosal wet weight, villus height, mucosal wall thickness, and mucosal protein in both the STD and alanyl-glutamine groups significantly decreased as compared with the control group. Furthermore, those parameters in the alanyl-glutamine group showed significant increases compared with STD group. Crypt depth showed no significant difference among the groups.

Mucosal DNA content in the STD group decreased significantly ($p < 0.05$) as compared with the control or alanyl-glutamine groups, but there were no significant differences between alanyl-glutamine and control groups.

Mucosal RNA content in the STD and alanyl-glutamine groups were significantly decreased ($p < 0.05$) as compared with control group; however, this parameter increased significantly in the alanyl-glutamine group ($p < 0.05$) as compared with the STD group.

Intestinal Absorptive Capacity and Permeability (Table 2)

Intestinal absorptive capacity studies with SMV D-xylose concentration showed no significant difference among the groups. However, permeability studies with plasma FITC-dextran concentration significantly increased ($p < 0.05$) in the STD group as compared with the control or the alanyl-glutamine group. No significant difference was observed between the control and alanyl-glutamine groups.

Intestinal Blood Flow and Glutaminase Activity (Table 3)

Glutaminase activity in jejunal mucosa of the STD group was significantly decreased ($p < 0.05$) as compared with the control and alanyl-glutamine groups. However, no significant difference was observed between the control and alanyl-glutamine groups.

Intestinal blood flow in both the alanyl-glutamine group and the STD group increased significantly ($p < 0.05$) as compared with the control group. In the alanyl-glutamine group, absolute intestinal blood flow increased by 13% compared with STD group, but this did not reach statistical significance.

Intestinal Amino Acid Metabolism (Table 4)

The AA–SMV glutamine difference in the alanyl-glutamine group exceeded ($p < 0.05$) that in the STD group. However, there was no difference among the groups in the percent fractional extraction of glutamine by the intestine.

An increased ($p < 0.05$) intestinal glutamine flux was noted in the alanyl-glutamine group as compared with the control and STD groups. Concomitant with increased intestinal net uptake of glutamine, there was no significant difference of net intestinal release of alanine in the alanyl-glutamine group, as compared with the control and STD groups. Intestinal net output of alanine was found to be significantly decreased ($p < 0.05$) in the STD group as compared with the control group.

DISCUSSION

Glutamine is the principle fuel used by the gastrointestinal tract,[6] with most of the uptake occurring in small intestinal epithelial cells that line the villi.[17,18] The small intestine of the rat is reported to extract approximately 25% of circulating glutamine.[19] The mucosal cells have high glutaminase activity consistent with their avid rate of uptake and metabolism.[20] The activity of glutaminase, a principle enzyme that catalyzes the hydrolysis of gluta-

Table 3. INTESTINAL BLOOD FLOW AND GLUTAMINASE ACTIVITY

	Intestinal GLNase (μmol/mg protein/hr)	Intestinal Blood Flow (mL/100g/min)
Control group (n = 8)	9.2 ± 2.9	7.2 ± 1.1
STD group (n = 9)	5.7 ± 1.7*†	8.4 ± 0.7*
Ala-Gln group (n = 9)	8.4 ± 1.2	9.1 ± 0.4*

STD = rats receiving total parenteral nutrition supplemented with conventional amino acid mixture; Ala-Gln = rats receiving alanyl-glutamine-supplemented total parenteral nutrition.
All values = mean ± SD
* $p < 0.05$ vs. Control group.
† $p < 0.05$ vs. Ala-Gln group.

Table 4. INTESTINAL GLUTAMINE AND RELATED SUBSTRATES METABOLISM

	AA (μmol/L)	AA-SMV (μmol/L)	Intestinal Extraction (%)	Flux (nmol/100gBW/min)
Glutamine				
Control group (n = 8)	551 ± 126	139 ± 57	24 ± 5	1008 ± 425
STD group (n = 9)	571 ± 137	116 ± 41	20 ± 4	966 ± 287
Ala-Gln group (n = 9)	723 ± 130*†	179 ± 69†	24 ± 5	1659 ± 700*†
Alanine				
Control group (n = 8)	278 ± 126	−183 ± 99	−64 ± 21	−1370 ± 849
STD group (n = 9)	289 ± 101	−79 ± 48*	−30 ± 19*	−657 ± 401*
Ala-Gln group (n = 9)	289 ± 125	−92 ± 35*	−37 ± 20*	−849 ± 341

AA = abdominal aorta; SMV = superior mesenteric vein; BW = body weight; STD = rats receiving total parenteral nutrition supplemented with conventional amino acid mixture; Ala-Gln = rats receiving alanyl-glutamine-supplemented total parenteral nutrition.
All values = mean ± SD.
* $p < 0.05$ *vs.* Control group
† $p < 0.05$ *vs.* STD group.

mine, generally is accepted as a marker of intestinal glutamine consumption, as evidenced by its tendency to decrease in the current study in rats with TPN supplemented with amino acid other than alanyl-glutamine, and by its increase with alanyl-glutamine feeding or treatment with glucocorticoid.[21,22] There is evidence that the activity of glutaminase tends to increase with glutamine feeding in the nonseptic condition.[23] Dudrick et al.[24] reported that intestinal glutaminase activity is preserved when a glutamine-containing diet is given for 4 days before endotoxin challenge in rats. They found a 25% increase in mucosal glutaminase activity. The data presented in the present study showed that jejunal mucosal glutaminase activity was higher in rats in the alanyl-glutamine group than those in the control and STD groups. This suggested that glutamine supplementation could up-regulate the activity of mucosal glutaminase. The AA-SMV glutamine difference in the alanyl-glutamine group exceeded that in the STD group. However, there was no difference among the groups in the percent fractional extraction of glutamine by the intestine.

Accurate quantification of intestinal blood flow is essential for quantifying intestinal blood flow and calculating intestinal substrates flux during different metabolic conditions. For this purpose, a dye dilution technique[25] has been used exclusively. According to the principle of this method, continuous infusion of dye for 10 to 30 minutes of time via a tertiary branch of the mesenteric vein is necessary to reach plasma equilibrium. Furthermore, simultaneous drawing of a certain amount of blood from both the AA and the SMV is essential to obtain the intestinal blood flow. These procedures might alter regional hemodynamics in rats. As such, real intestinal blood flow and real calculated intestinal substrates flux may not be obtained. Therefore, in a previous study, we compared the intestinal blood flow obtained by dye dilution method with that of ultrasonic transit time flowmetry in the same experimental animals, and later, proposed an alternative method available for quantifying intestinal blood flow and to calculate intestinal substrates flux during various perturbation of the gut in rats, using the principle of ultrasonic transit time flowmetry.[26]

There are few reports about the measurement of intestinal blood flow in rats receiving TPN. The reason for increased intestinal blood flow in both TPN groups compared with the control group was not clear. This might be because the influence of continuous infusion of TPN solutions on circulation for a long time. Further investigation is needed to justify it. Concomitant with increased intestinal uptake of glutamine, there were no significant differences in net intestinal release of alanine in the alanyl-glutamine group, as compared with the other groups. This relationship may be associated with a concomitant increase in production of ammonia, for the liver to be used predominantly for ureagenesis and glutamine synthesis,[19] because early studies have verified that approximately 38% of glutamine nitrogen taken up by the bowel is converted into ammonia.[19] However, in the current study, we have learned that supplemental alanyl-glutamine enhanced the activity of glutaminase, increased glutamine consumption, and therefore, maintained mucosal metabolism.

Administration of TPN as the sole means of nutrition to healthy experimental animals is associated with progressive intestinal atrophy.[27-29] The atrophy is characterized by reduction of mucosal weight, villus height mucosal wall thickness, mucosal protein, and DNA and RNA content. In experimental animal models, supplementation of TPN solutions with 1% to 2% glutamine maintains small intestinal mass, nitrogen content, and villus

height.[10,11,30,31] However, In the current study, the addition of alanyl-glutamine increased the jejunal mucosal weight, villus height, mucosal wall thickness, protein, and DNA and RNA content compared with the STD group. The mechanism by which glutamine, as a single amino acid nutrient, exerted its trophic effect on intestinal mucosa of rats receiving glutamine-free TPN is unclear. However, the following explanation can be made. First, alanyl-glutamine increased glutamine uptake and consumption by the intestine, thereby supplying oxidative fuel and amide nitrogen; the latter might support in the synthesis of purines and pyrimidines,[32] suggesting the basis for the observed increase in weight, protein content, villus height, and DNA and RNA content in jejunal mucosal of rats with alanyl–glutamine-supplemented TPN in this study. Therefore, the provision of alanyl-glutamine could prevent deterioration of the intestinal cellularity by the supply of metabolic energy and nucleotide bases required for cellular division and replication. Second, glutamine could serve as a secretagogue, stimulating the release of peptide trophic hormones (*e.g.*, bombesin, neurotensin, enteroglucagon).[31,33] Li et al.[34] reported that an elevated concentration of glucagon was detected in the portal vein of rats receiving glutamine containing TPN. This hormone, according to Geer et al.,[35] is important in the regulation of glutamine consumption by increasing the specific activity of intestinal glutaminase that we observed in the mucosa in rats receiving TPN supplemented with alanyl-glutamine. These aforementioned hormones are known to play in several metabolic pathways in intestinal mucosa[36–39] and may account in part for the changes occurring in the intestine. In addition, the fact that the trophic effects of alanyl-glutamine on intestinal mucosa occurred in the absence of any oral food intake lends further support to the view that alanyl-glutamine may have an influence on intestinal humoral mechanism.

The intestinal mucosa normally functions as a barrier to intraluminal bacteria and noxious macromolecules, thus preventing their invasion into the submucosa, lymph node, systemic circulation, and other organs. Dysfunction of intestinal barrier during TPN, as evidenced by the promotion of bacterial translocation[40] and the increase of intestinal permeability,[41] has been reported recently. These findings may be of clinical importance in various disease conditions in which TPN currently is becoming an integrated part of patient management. Sepsis or endotoxemia of unknown origin during TPN may be the result of promotion of bacterial translocation or an increase of intestinal permeability. Small intestinal mucosa has the property to transport the nutrients from the lumen to the circulation, either by a carrier-mediated, facilitated mechanism or by a nonmediated mechanism, two distinct processes that may vary independently, but which together constitute absorption. Some authors defined the nonmediated diffusion as the term permeability.[42] Accordingly, permeability is that property of the intestinal epithelium or a membrane that refers to the facility with which it allows molecules to pass through by nonmediated diffusion—*i.e.*, the passage of molecules down a concentration gradient without the assistance of a passive or active biochemical carrier system.

For the assessment of barrier function of intestinal mucosa, a permeability test can be a suitable method. The D-xylose absorption test[43] has been used widely to assess small-intestinal absorption capacity. D-xylose, which is understood as being absorbed by enterocytes of the upper small intestine with the facilitated transport mechanism,[44] cannot be used to distinguish between mediated and nonmediated diffusion. For this purpose, a study with a D-xylose, lactulose, and mannitol combination recently has been reported in clinical cases.[45] In the current study, we used a D-xylose and FITC-dextran 70000 combination in rats to assess any alteration of intestinal absorptive capacity and permeability under TPN with or without alanyl-glutamine supplementation. The FITC-dextran 70000, has been used as a probe to assess intestinal permeability in rats during total parenteral nutrition.[41,46]

Because of the metabolism of D-xylose by the liver,[47] we chose to measure the concentration of D-xylose in SMV blood as a more accurate indication of enterocyte function as compared with measuring D-xylose in the systemic circulation. We found that intestinal absorptive function of D-xylose was not significantly different among the groups in this study, whereas plasma FITC-dextran in the STD group increased significantly compared to the control and alanyl-glutamine groups. The reason for increased plasma FITC-dextran in the STD group, despite insignificant changes in SMV D-xylose concentration observed in this study, may be explained as follows. D-Xylose is absorbed by a facilitated transport mechanism.[47] Its absorption also depends on intestinal blood flow.[47] In this study, both the STD and alanyl-glutamine groups were provided with isocaloric TPN solutions, and intestinal blood flow also was maintained in both groups. These two factors may continuously provide sufficient energy to the mucosal cells in the STD and alanyl-glutamine groups to absorb D-xylose without any significant change, despite significant alterations in mucosal structure compared with the control group. However, if the problem was only of mucosal structure and hence, permeability changes, as evidenced by increased plasma concentration of FITC macromolecule in the STD group, an increase in SMV D-xylose should have occurred. Therefore, we have learned that D-xylose absorption tests may not be a good marker for

the assessment of intestinal barriers function in villus atrophy. However, increased plasma FITC dextran was found to be associated with mucosal atrophy in the STD group. Therefore, an increased plasma FITC-dextran level in the STD group with altered villus structure may indicate increased "leakiness" of the intercellular complex to macromolecule independent of the immune system. Adding alanyl-glutamine to TPN solutions prevented the increase in plasma FITC-dextran, which was associated with improved mucosal structure. An association of lack of luminal mucous gel layer and the increase of plasma FITC-dextran in TPN group rats recently has been noted.[46] Whether provision of alanyl-glutamine to the TPN maintains mucous gel layer and thereby decreases FITC permeability is not known. Further study is necessary in this respect.

Supplementation of TPN with alanyl-glutamine increased intestinal glutaminase activity with increased intestinal uptake of glutamine, and improved the morphology of jejunal mucosa. In addition, it decreased intestinal permeability of the macromolecule FITC-dextran. Thus, the addition of alanyl-glutamine dipeptide to parenteral solution improves intestinal glutamine metabolism, and prevents deterioration of mucosal structure and permeability in rats.

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