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Shosaku Hayashi*

*Okayama University,

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EXPERIMENTAL STUDIES ON NUTRITION MANAGEMENT IN LIVER INJURY

Shosaku HAYASHI

First Department of Internal Medicine, Okayama University Medical School, Okayama 700, Japan (Director: Prof. H. Nagashima)

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Abstract. Preventive and therapeutic effects of nutrition management on acute and chronic liver injury were experimentally studied with rats. A branched-chain amino acids (BCAA)-enriched solution and a commercially available amino acid solution with and without glucose were comparatively tested to investigate the efficacy of the BCAA-enriched solution. Administration of the amino acid-glucose solution prevented acute liver injury induced by either carbon tetrachloride (CCl_4) or D-galactosamine (GalN), and also accelerated the repair of acute CCl_4 liver injury. In cirrhotic rats, the BCAA-enriched amino acid-glucose solution was more effective in improving abnormal values of the Hepaplastin test, Indocyanine green (ICG) clearance and nitrogen balance than that of either a glucose or electrolyte solution. Preadministration of the BCAA-enriched solution to cirrhotic rats suppressed the appearance of coma and abnormal behavior observed following ammonia acetate loading. No essential difference in the enteral or intravenous administration of the nutrients was observed. These results support the idea that nutrition management in severe liver disease can be performed effectively and safely by enteral or intravenous infusion of the BCAA-enriched solution.

Key words: severe liver injury, nutrition management, amino acid, enteral administration, intravenous administration.

Anorexia, ascites, intestinal bleeding and hyperammonemia are frequently the major problems in the care of patients with severe liver diseases such as fulminant hepatitis and decompensated liver cirrhosis. Impaired intestinal absorption and abnormal metabolism of various nutrients are also difficulties. Long-term fasting or low protein diets often cause protein-calorie malnutrition, and in fact, diminished calorie and protein intake has been reported in alcoholic and nonalcoholic chronic liver diseases (1, 2). Malnutrition may induce the worsning of liver dysfunction, since the liver play a central role in digestion, metabolism and strage of nutrients.

An increase in aromatic amino acids (AAA) and methionine concentrations and a decrease in BCAA levels in the blood are characteristic of patients and experimental animals with hepatic insufficiency (3, 4). Such abnormal plasma aminograms are considered to be causally related to hepatic encephalopathy (5). Improvement of the plasma amino acid balance may have a beneficial effect on encephalopathy as well as providing better nutrition. Fischer *et al.* (6) have al-

ready used a special amino acid solution containing an increased amount of BCAA and a decreased amount of AAA and methionine to normalize the abnormal plasma amino acid concentrations in patients with severe liver disease.

The enteral and parenteral administration of a synthetic amino acid-glucose solution has been adequate therapy for seriously ill patients (7, 8). Total parenteral nutrition (TPN) and elemental diet (ED) are representative methods of clinical nutritional support. Enteral feeding is more physiological, safer and easier than intravenous hyperalimentation in which direct effects of the nutrients supplied through the portal vein on the injured liver can be expected. We have already evaluated the effects of nutrition management by both the parenteral and enteral routes with a BCAA-enriched solution in patients with severe liver disease (9, 10). Few comparative studies on the treatment of patients by TPN and ED are to be found.

In the present study, effects of nutrition management by enteral and intravenous administration using two different amino acid solutions (BCAA-enriched and commercial type) are investigated in liver-injured rats.

MATERIALS AND METHODS

Animals. Male Sprague-Dawley rats weighing 150 to 450 g were used and maintained at a constant temperature (25 ± 3℃) on Oriental Laboratory Chow MF. A polyethylene catheter with an outer diameter of 1.1 mm was inserted under light ether anesthesis into the external jugular vein for intravenous feeding or into the duodenum by a standard gastrostomy (11). Nutrients were continuously fed using a perista pump at a flow rate of 2 ml per h. Following operation, rats were placed in an individual metabolic cage without restraint. Neither nutrients nor water except for the infused materials was given to the rats during the experiment. Urine was collected everyday. For inducing acute liver injury, 20 % CCl_4 in liquid paraffin was administered intragastrically to overnight-fasted rats with a body weight of 270 to 320 g at a dose of 1.0 ml per 100 g body weight in Experiment Ⅰ and Ⅳ as described under "Experimental series" or 0.8 ml per 100 g body weight in Experiment Ⅱ. Aqueous solution of GalN was neutralized with 2 N NaOH and injected intraperitoneally to overnight-fasted rats weighing 150 to 170 g at a dose of 130 mg per 100 g body weight. For inducing liver cirrhosis, 50 % CCl_4 solution in olive oil was injected subcutaneously into rats twice a week for 12 weeks at a dose of 0.1 ml per 100 g body weight, and a 0.05 % phenobarbital solution was supplied as drinking water in order to obtain cirrhosis rapidly. The body weight of these rats increased from 150 g initially to approximately 400 g when cirrhosis of the liver was microscopically confirmed. Rats weighing 400 g were used as controls for this experiment. Cirrhotic animals showed hyperammonemia (cirrhotics: 114 ± 40 μg/dl and controls: 22 ± 2, $p < 0.01$), very low Hepaplastin test values (54 ± 12 % and 78 ± 9, $p < 0.05$) and also very low ICG clearance (0.086 ± 0.011 and 0.150 ± 0.040, $p < 0.05$). Histological observation of the liver revealed typical cirrhosis, that is, a pseudolobule with an annular configuration and round cell infiltration in the connective tissues (See Fig. 1).

Experimental series. Experiment Ⅰ was performed in order to study the preventive effect of a preinfusion with the amino acid-glucose solution prior to CCl_4 or GalN administration on acute liver injury. The chemical composition of the different solutions are shown in Table 1. These solutions were continuously administered either intraduodenaly or intravenously for 24 h

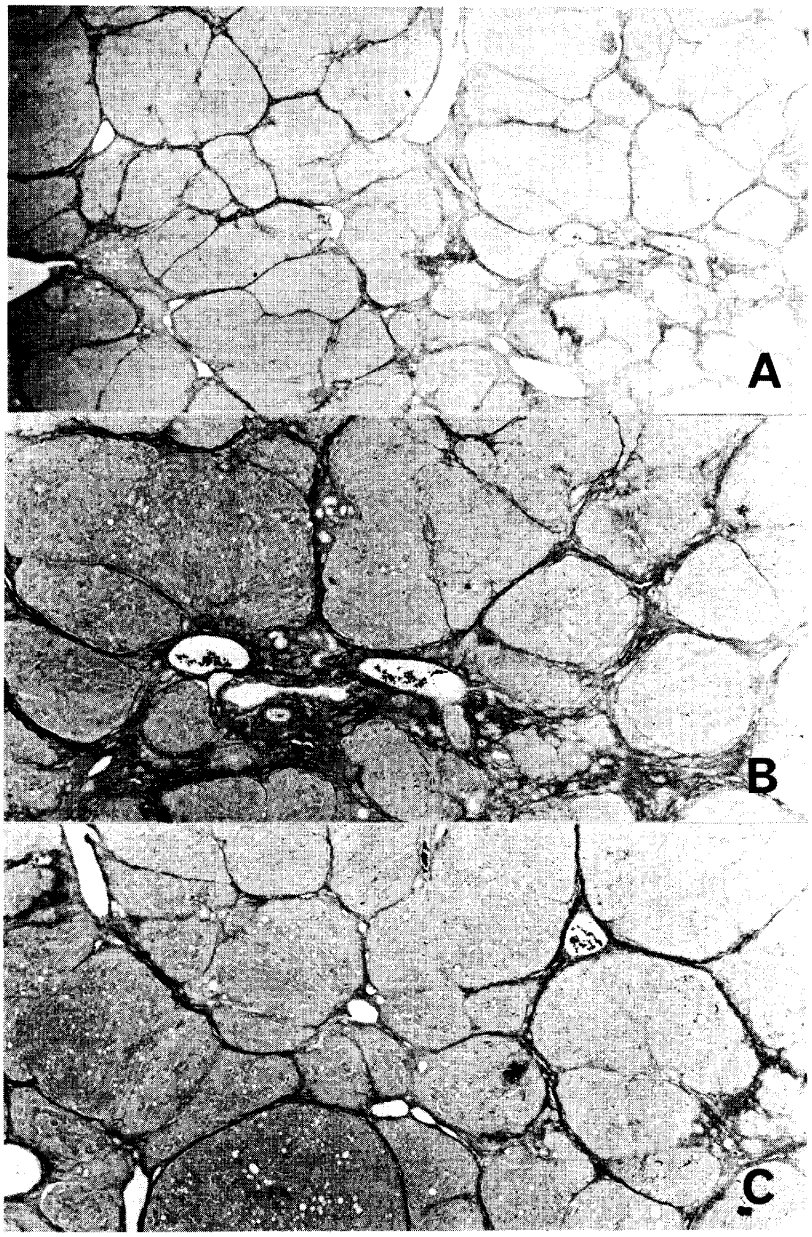

Fig. 1. Histological observations of the liver in cirrhotic rats before and after nutrition management (× 100, Azan, Experiment Ⅲ). Pseudlobular nodules are revealed prior to the experiment (A). Microscopic findings of the liver in cirrhotic rats treated with the BCAA-enriched amino acid-glucose solution by the intravenous (B) or enteral route (C). Other procedures are described under "Materials and Methods".

as described under "Animals", after which CCl_4 or GalN was administered. Immediately after CCl_4 or GalN administration, each solution was switched to electrolyte alone, and the feeding was continued for 24 h. Experiment II was carried out to investigate the effect of infusing the nutrients enterally or intravenously on the repair of acute liver injury. CCl_4 was administered intragastrically to overnight-fasted rats, and an electrolyte solution was infused for the next 24 h. Then the BCAA-enriched amino acid-glucose solution or electrolyte solution was administered enterally or intravenously for 24 h to the rats with acute liver injury. The purpose of experiment III was to examine the therapeutic value of nutrition management in cirrhotic rats. The last CCl_4 injection was carried out 3 days prior to to the experiment. Four different solutions (A, D, E and F in Table 1) were continuously infused enterally or intravenously for 5 days into cirrhitic rats. Experiment IV was performed to test the preventive effect of preadministration of the BCAA-enriched solution on ammonia-induced encephalopathy in rats with acute and chronic liver injury. CCl_4 was given intragastrically 12 h before enternal infusion of an 8 % BCAA-enriched solution (G in Table 1) for 24 h. Ammonium acetate was then injected intraperitoneally in a single dose of 0.3 mmoles per 100 g body weight, which did not induce behavior abnormalities in control rats. Blood ammonia levels were determined before, 40 and 80 min after, and the behavioral abnormalities of the rats were observed for 90 min after the injection of ammonium acetate, following Higashi's criterion (12).

Analytical procedure. Blood ammonia levels were measured according to an enzymatic method (13) (Experiment I to III) and an ultradiffusion method (14). Serum immunoreactive insulin (IRI) and plasma immunoreactive glucagon (IRG) concentrations were determined by radioimmunoassay using 30 K antibody (15, 16). The ICG clearance test was performed by injecting 0.05 mg indocyanine green per 100 g body weight. The ICG clearance value was expressed as K_{ICG}. Quantitative analyses of serum amino acids were carried out using an amino acid analyzer as reported previously (17). Nitrogen balance, liver triglyceride contents,

TABLE 1. CHEMICAL COMPOSITIONS OF THE DIFFERENT SOLUTIONS USED THROUGHOUT THE EXPERIMENTS

	Solution						
	A	B	C	D	E	F	G
Glucose (g/dl)	200	None	None	200	200	None	None
Amino acid (g/dl)	None	40.1[a]	42.0[b]	40.1[a]	42.0[b]	None	84.0[b]
Total nitrogen (g/dl)	None	11.7	12.2	11.7	12.2	None	24.5
Electrolyte (mEq/l)							
Na	65	64	59	64	59	65	14
Cl	55	86	69	86	69	55	94

The 20 % glucose solution (A), the 4 % commercially available amino acid solution (B), the 4 % BCAA-enriched solution (C), the 4 % commercially available amino acid-20 % glucose solution (D), the 4 % BCAA-enriched amino acid-20 % glucose solution (E), the electrolyte solution (F) and the 8 % BCAA-enriched solution (G).

a) The commercially available amino acid solution : amino acid compositions are shown in parentheses in *b)* mentioned below.

b) Amino acid compositions of the BCAA-enriched solution are as follows (g/dl): leucine 11.0 (7.8), valine 8.4 (5.8), isoleucine 9.0 (5.6), methionine 1.0 (3.6), phenylalanine 1.0 (8.6), tryptophan 0.7 (1.4), threonine 4.5 (4.0), lysine 7.5 (7.0), arginine 7.3 (8.0), histidine 3.2 (4.0), alanine 7.5 (3.2), proline 8.0 (1.6), cysteine 0.4 (0.2), glycine 9.0 (0) and serine 5.0 (1.6).

serum GPT activity and Hepaplastin test values were determined routinely. Changes in the body weight (%) were calculated as [(body weight after infusion/body weight before infusion) $\times 100$] and the relative liver weight (%) as [(liver weight/body weight) $\times 100$]. Specimens of the liver were stained with Hematoxylin-Eosin and Azan.

The obtained data were expressed as mean ± standard deviation of the mean, and significance was evaluated by Student's t-test.

RESULTS

Effects of preadministration of an amino acid and/or glucose solution on acute liver injury. Rats, which received the BCAA-enriched solution in glucose enterally or intravenously for 24 h prior to CCl_4 administration, maintained body weight fairly well during this experiment. The enteral or intravenous preadministration of either amino acids or glucose was not sufficient for maintaining body weight. In rats enterally preadministered with either the commercially available amino acid solution or the BCAA-enriched solution, the gain in relative liver weight was significantly ($p < 0.05$) more than in those rats infused enterally with the amino acid solution in glucose or the electrolyte solution (Table 2). The reasons why the liver did not enlarge in rats infused with the amino acid-glucose solution and the electrolyte solution alone ought to be different, since liver damage would be partially inhibited by the simultaneous administration of amino acids with glucose and the liver glycogen in rats which received electrolyte alone for 48 h would be used up. Blood ammonia levels were much higher in the unnourished rats (Fig. 2) and ele-

TABLE 2. EFFECTS OF THE PREADMINISTRATION OF VARIOUS SOLUTIONS BY THE ENTERAL OR INTRAVENOUS ROUTE ON ACUTE CCl_4 LIVER INJURY

Route and solution	Change in body weight (%)	Relative liver weight (%)	Liver triglyceride (mg/g wet liver)	Serum IRI (μU/ml)	Plasma IRG (pg/ml)
Enteral administration					
A	88± 1	3.8±0.3	14.2± 9.3	26.0±21.7	135± 51
B	88± 2	4.0±0.2	n.d.	19.1± 6.0	128±100
C	87± 1 *	4.0±0.2 * *	n.d.	32.7±24.6	198± 81 * *
D	92± 2 * *	3.4±0.3 * * *	n.d.	14.8± 4.2 *	90± 17
E	96± 3 *	3.3±0.2 *	20.6±10.6	19.1± 6.0 *	256±143 *
F	88± 2 *	3.4±0.2	29.9± 4.4	66.8±31.1 *	281± 92
Intravenous administration					
A	92± 6	4.0±0.1	17.4± 1.1	37.0±21.7	168±164
D	93± 4	4.1±0.3	n.d.	17.8±12.6	81± 75
E	95± 3	4.0±0.4	21.5± 8.9	19.6±11.6	167± 64
F	89± 4	3.9±0.4	25.4± 8.9	72.3±41.0	302±142

Four rats were examined in each group. Expressed as Mean±S.D. n.d.: Not determined.
* $p < 0.05$ ** $p < 0.01$

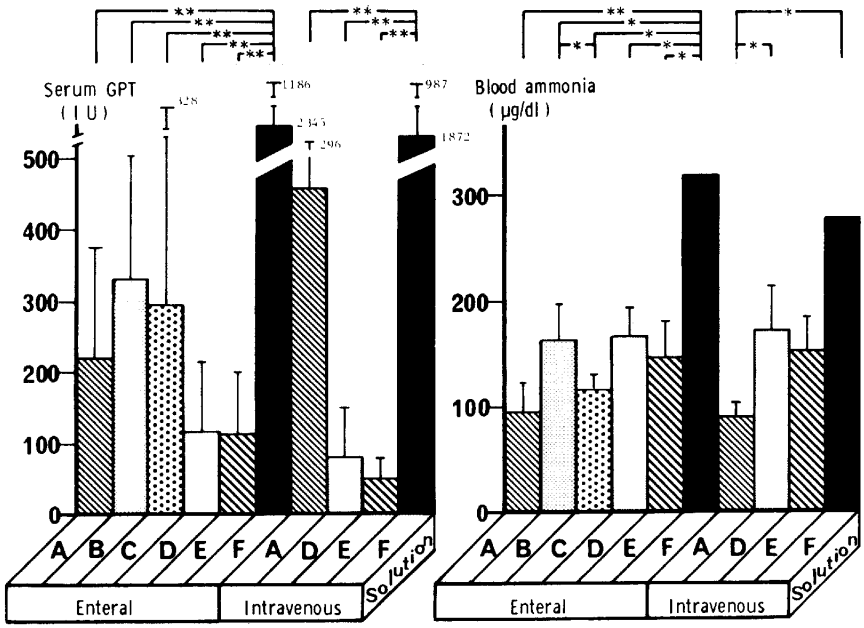

Fig. 2. Serum GPT activity and blood ammonia levels in CCl_4-treated rats (Experiment 1). Four animals are used in each group. The nutritional components of the different solutions (A, B, C, D, E and F) are described in Table 1. Vertical line on each bar indicates the standard deviation of the mean. Values beside the bars indicate serum GPT activity beyound the scale. Significant difference between each experimental group is shown at the top of the figure: $p < 0.05$, *; $p < 0.01$, **; and $p < 0.001$, *** (these marks are used similarly in the following figures).

vated in the electrolyte-administered group. Blood ammonia levels were significantly higher ($p < 0.05$) in rats administered the commercially available amino acid solution than in rats given the BCAA-enriched solution, although total nitrogen contents were similar. A marked elevation of serum GPT activity was observed in rats enterally or intravenously treated with electrolyte alone (Fig. 1). The simultaneous administration of amino acids and glucose (D, E) was more effective in preventing the elevation of serum GPT activity than treatment with either amino acids or glucose alone. A difference of serum GPT activity in rats between those infused enterally and those infused intravenously was not observed. Liver triglyceride contents increased in rats which received electrolyte alone either route with no significant difference between the two routes (Table 2). Serum IRI and plasma IRG levels increased in CCl_4-treated rats infused with electrolyte. Serum AAA and BCAA levels increased in rats given no nutrient, suggesting the occurence of severe liver injury (Fig. 3). Serum AAA and BCAA levels were slightly lower in rats which received the BCAA-enriched amino acid-glucose solution than in rats given electrolyte alone, which suggests the nutrients had some preventive effect on acute liver injury. It is well known that the serum aminogram is influ-

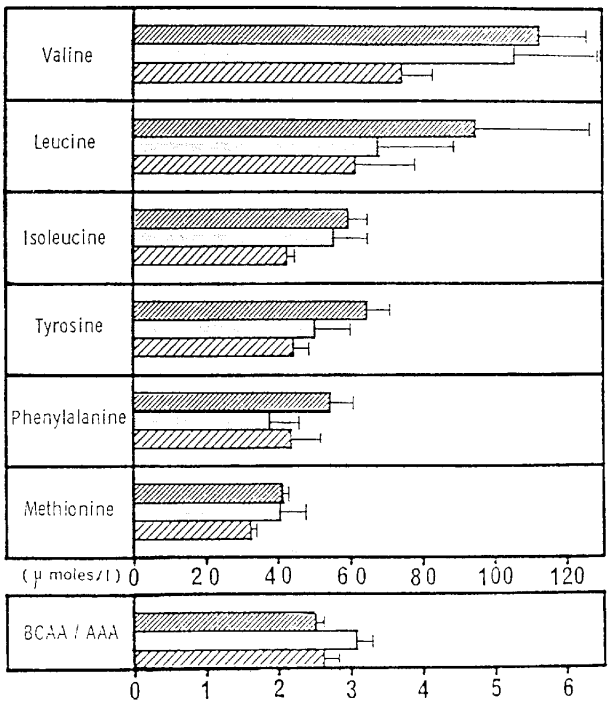

Fig. 3. Serum neutral amino acid concentrations in CCl_4-treated rats (Experiment 1). The BCAA-enriched amino acid-glucose solution (E) is administered for 24 h by means of the enteral (▭) or intravenous route (▨) and the electrolyte solution (F) by the enteral route (▨). Then CCl_4 is given. The solution is then changed to the electrolyte solution. A blood sample is collected 24 h after CCl_4 treatment. Four rats are used in each group. Horizontal bars indicate the mean values of each group, and the lines to the right side of each bar show the standard deviation of the mean.

enced directly by the amino acid composition of the infused solution, therefore determination of the serum amino acid concentrations was not carried out in the following experiment, because administration of the amino acid solution was continued until just before blood samples were collected. Necrosis of the hepatocytes in the liver from rats treated with electrolyte alone (Fig. 4) was massive, but moderate in rats which received the amino acid-glucose solution. Similarly, preadministration of the BCAA-enriched amino acid-glucose solution prevented acute GalN liver injury since blood ammonia and serum GPT levels were more depressed in rats treated with the BCAA-enriched amino acid-glucose solution than in those treated with electrolyte alone (Fig. 5). Treatment with the BCAA-enriched amino acid-glucose solution prevented hepatic necrosis in GalN as well as CCl_4-intoxicated rats.

Effects of enteral or intravenous administration of the amino acid-glucose solution on the repair of acute liver injury. Changes in body weight and relative liver weight were not significantly altered in the four groups of CCl_4-intoxicated rats with either

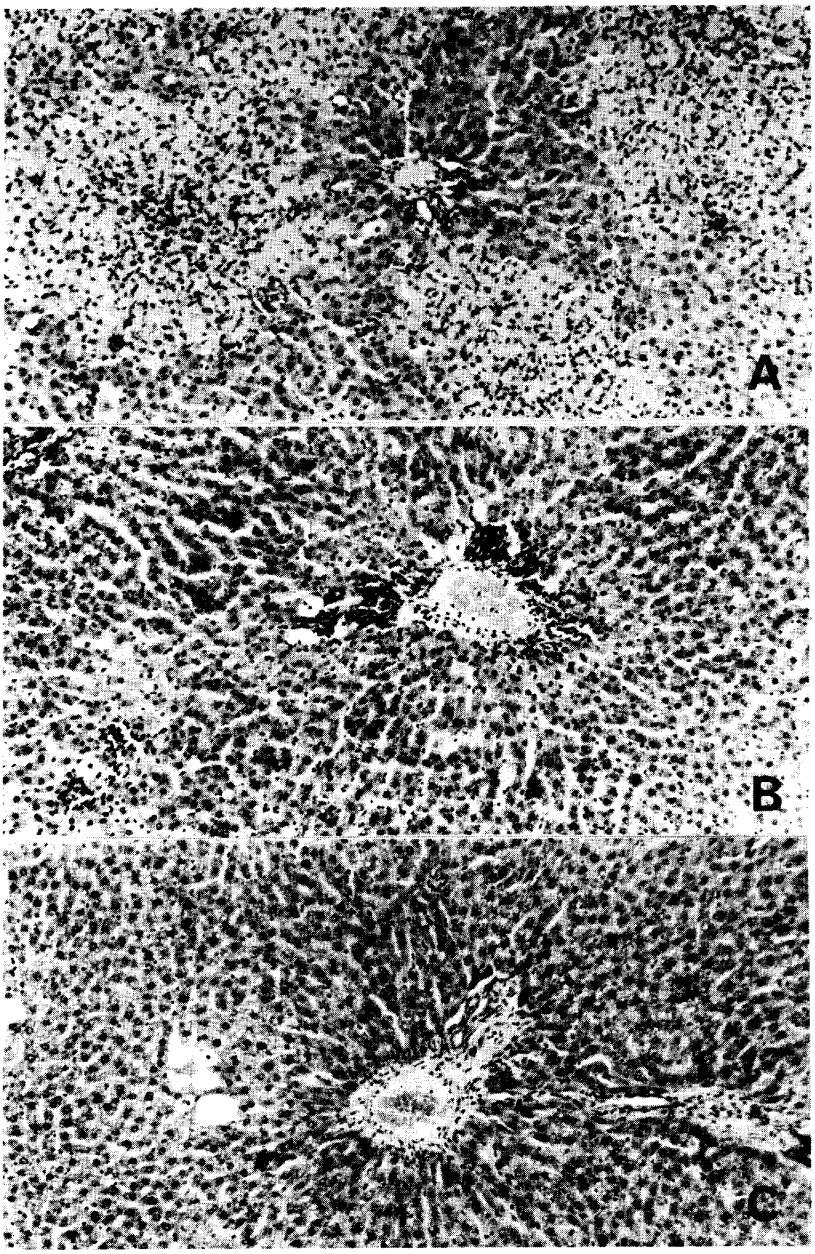

Fig. 4. Histological findings of the livers of CCl_4-treated rats (× 100, H & E, Experiment 1). Massive necrosis of the hepatocytes is observed in the livers of rats treated with electrolyte solution via the enteral route (A). Cell infiltrations in the portal area are found in the liver of rats which received the BCAA-enriched amino acid-glucose solution by the intravenous route (B), but seldom in those treated by the enteral route (C).

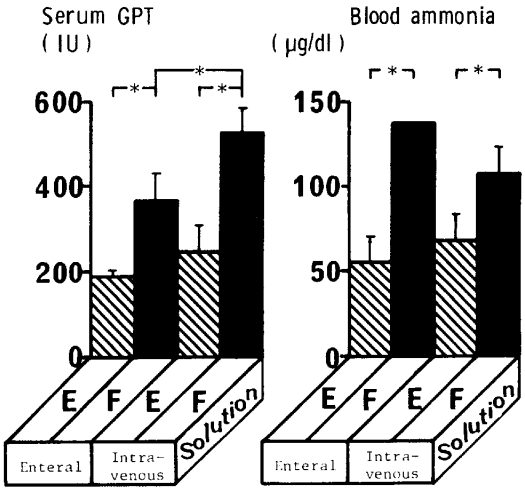

Fig. 5. Serum GPT activities and blood ammonia levels in GalN-treated rats (Experiment I). Four animals are used in each group. The BCAA-enriched amino acid-glucose solution (E) or the electrolyte solution (F) is enterally or intravenously preadministered to rats. Vertical lines on each bar indicate the standard deviation of the mean.

TABLE 3. EFFECTS OF THE ENTERAL OR INTRAVENOUS ADMINISTRATION OF THE BCAA-ENRICHED AMINO ACID-GLUCOSE SOLUTION AND THE ELECTROLYTE SOLUTION ON ACUTE CCl_4 LIVER INJURY

Route and solution	Change in body weight (%)	Relative liver weight (%)	Serum IRI (μU/ml)	Plasma IRG (pg/ml)
Before the start of infusion	100	4.0± 0.1	24.0± 3.9	219± 61
Enteral administration				
E	98± 1	4.1± 0.3	133.2± 49.0 *	219± 52
F	96± 2	3.8± 0.2	16.4± 3.5 *	178± 38
Intravenous administration				
E	99± 1	4.0± 0.2	139.6± 35.4 *	284± 75
F	96± 2	4.3± 0.1	20.1± 2.0 *	164± 41

Four rats were examined in each group. * $p < 0.01$

enteral or intravenous administration of the nutrients (Table 3). Serum GPT activity increased markedly (3085 ± 1165 IU) in all four groups 24 h after CCl_4 was injected into rats which indicated that liver damage had occurred. In rats infused enterally with the BCAA-enriched amino acid-glucose solution, serum GPT activity was significantly lower ($p < 0.05$) than those infused intravenously (Fig. 6). Serum IRI elevation was significantly greater ($p < 0.001$) in the rats receiving nutrients by either route than those not receiving nutrients, probably because of the glucose administration just prior to obtaining the blood sample (Table 3). Plasma

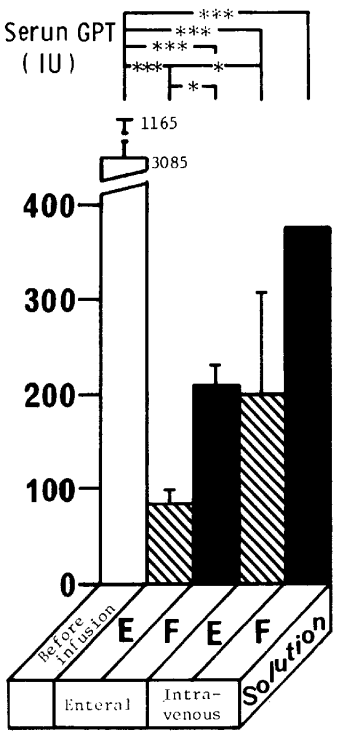

Fig. 6. Serum GPT activities in CCl_4-treated rats (Experiment II). Four animals are used in each group. Vertical bars and lines on each bar indicate the mean and standard deviation, respectively. CCl_4 is given to overnight-fasted rats. Serum GPT activities increased markedly 24 h after treatment (shown as "Before infusion" in this figure). Then, the BCAA-enriched amino acid-glucose solution (E) or the electrolyte solution (F) is infused enterally or intravenously for 24 h. Blood samples are collected 48 h after CCl_4 administration. Although the activities decreased gradually in rats infused with electrolyte, they decreased more in rats which received the BCAA-enriched amino acid-glucose solution.

IRG levels in rats infused with the nutrients were slightly higher than those in rats with electrolyte alone, although the differences were not significant.

Effects of nutrition management on chronic liver injury. Cirrhotic rats which received electrolyte alone for 5 days showed significant body weight ($p < 0.05$) (Fig. 7) and liver weight (Table 4) loss as compared to those which received glucose either with or without the two different types of amino acid solution, regardless of whether administered enterally or intravenously. In nutrient-administered rats, on the other hand, the relative liver weight did not change significantly during the experiment. Serum GPT activity in cirrhotic rats infused with electrolyte was higher ($p < 0.05$) than those in rats either type of amino acid solution in glucose (Table 4). Blood ammonia levels were much higher in rats which received the commercially available amino acid solution in glucose than those in rats infused with electrolyte, glucose or the BCAA-enriched amino acid-glucose, with no significant difference between enteral and intravenous administration (Table 4). Serum IRI levels were lower in electrolyte-administered rats than those in rats treated with glucose and/or the amino acid solutions by either route (Table 4), probably because no nutrient was given. In all the groups, there was no significant change in the plasma IRG levels, although the levels tended to be higher in the two groups of rats infused with electrolyte probably because of maintaining blood sugar levels. A distinked negative nitrogen balance was seen in rats not treated with the amino acid solu-

TABLE 4. EFFECTS OF THE ENTERAL OR INTRAVENOUS ADMINISTRATION OF VARIOUS SOLUTIONS FOR 5 DAYS ON LIVER CIRRHOSIS

Route and solution	No. of rats	Relative liver weight (%)	Blood ammonia (μg/dl)	Serum GPT (IU)	Serum IRI (μU/ml)	Plasma IRG (pg/ml)
Enteral administration						
A	4	4.0± 1.0	96± 32	68± 29	32.4± 21.4	152± 81
D	7	4.4± 0.4	137± 29	46± 22	26.4± 19.3	178± 54
E	6	4.4± 0.9	94± 4 *	28± 13 *	23.8± 20.6	127± 13
F	8	3.6± 0.4	98± 22	122± 36 *	11.0± 3.2	258± 212
Intravenous administration						
A	4	4.0± 0.3	80± 14 *	53± 40	48.3± 24.8	168± 112
D	4	4.4± 0.1	149± 6 * *	44± 19	51.9± 37.0	192± 69
E	4	4.5± 0.4 * *	119± 11 * *	47± 28 *	60.2± 34.0	199± 119
F	4	3.5± 0.1 * *	81± 13 * *	139± 8 *	10.9± 7.5	274± 120

* $p < 0.05$, ** $p < 0.01$

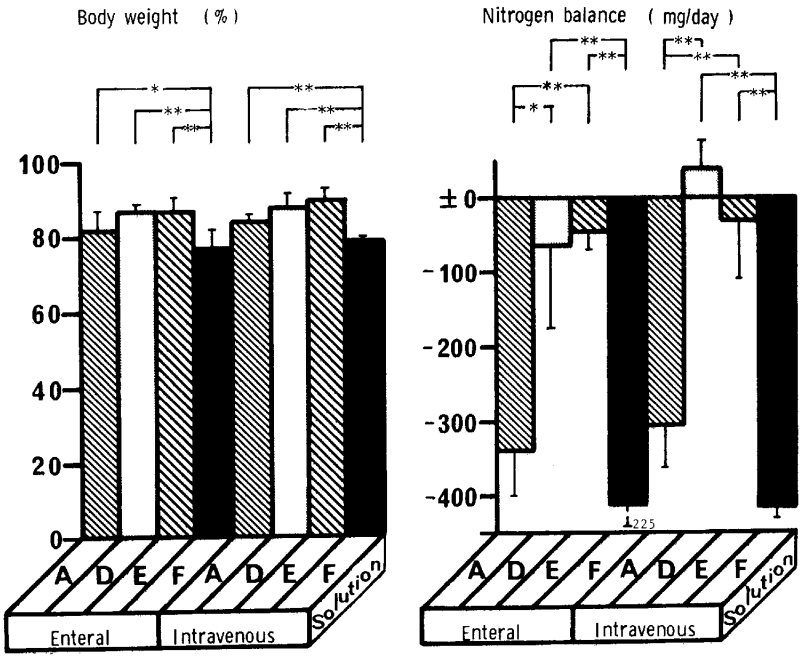

Fig. 7. Changes in body weight and nitrogen balance in cirrhotic rats treated with the various solutions (Experiment III). The number of rats examined in each group is shown in Table 4.

tions. Furthermore, the Hepaplastin test and ICG clearance values were low even when the commercially available amino acid-glucose solution was infused, these

values being significantly different ($p < 0.05$) from those when the BCAA-enriched solution in glucose was administered, in which case the values before and after infusion were similar (Fig. 8). Severe liver cell atrophy and proliferation of the connective tissues were found in cirrhotic rats which received electrolyte alone, the commercially available amino acid or the BCAA-enriched solution in glucose.

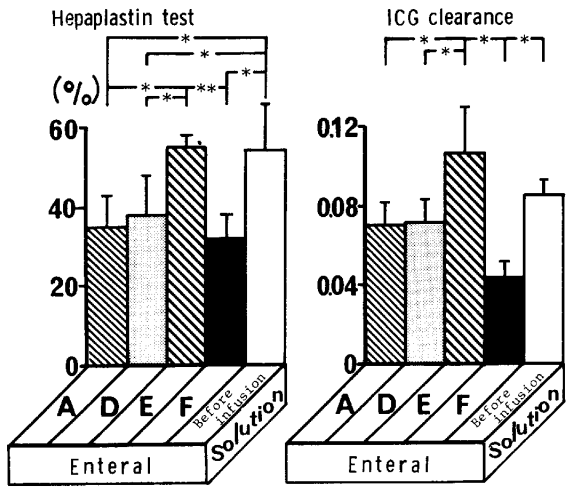

Fig. 8. Hepaplastin test and ICG clearance values in cirrhotic rats before and after nutrition management by the enteral route (Experiment III).

TABLE 5. EFFECTS OF THE ENTERAL ADMINISTRATION OF THE BCAA-ENRICHED SOLUTION ON BEHAVIOR CHANGE AND BLOOD AMMONIA LEVEL FOLLOWING AMMONIUM ACETATE INJECTION

Solution and group	No. of rats	Died	Behavior*		Blood ammonia (μg/dl)		
			Coma	Alert	Before	After ammonia load 40 min.	After ammonia load 80 min.
F							
Untreated	3	0	0	2	13± 5	184± 55	56± 24
Acute liver injury	4	0	1	2	151± 70	296± 130	218± 124
Liver cirrhosis	6	2	5	0	118± 44	349± 74	322± 79
G							
Untreated	3	0	0	3	27± 14	87± 31	33± 20
Acute liver injury	4	0	1	2	84± 49	270± 132	221± 169
Liver cirrhosis	6	0	2	3	136± 50	318± 75	259± 70

* Behavior change according to Higashi's criterion (Ref. 12). Mean± S.D. is shown.
* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

There was no significant difference in the histology of the liver between enterally and intravenously treated rats.

Preventive effects of the BCAA-enriched solution on ammonia-induced encephalopathy. Five out of 6 cirrhotic rats, to which electrolyte alone was preinfused into the duodenum, fell into a deep coma (Table 5). Two out of the 5 comatose rats with cirrhosis died within 90 min following the ammonium acetate injection. However, no cirrhotic rats died in the experimental group which received the 8 % BCAA-enriched solution, and only 2 out of the 6 rats in this group fell into a coma; after which there was complete recovery. There were 3 cirrhotic rats in the BCAA-treated group without abnormal behavior, but none in the electrolyte-administered group. The preventive effect of the enteral preadministration of the BCAA-enriched solution was not observed in rats with acute CCl_4 injury. Blood ammonia levels in cirrhotic and acute liver-injured rats treated or not treated with amino acids were much higher than those in control rats with normal liver function. Blood ammonia levels following ammonium acetate injection decreased rapidly in control rats, but the levels in liver-injured rats remained high at least until 80 min following the ammonium acetate loading. The waves were slow with high amplitude in the electroencephalograms of rats which fall into coma.

DISCUSSION

It has been reported that daily calorie, protein and vitamin uptake diminishes in patients with severe liver disease, and consequently protein-calorie malnutrition takes place (18, 19). The importance of nutrition management in severe liver disease for clinical improvement of the general condition, repair of liver injury and also prevention of hepatic failure is recognized. However, suitable and effective nutrition management has not been developed yet for treatment of liver disease. Suitable nutrients, their proper dose and the best way to administer them to patients with severe liver diseases such as fulminant hepatitis and decompensated liver cirrhosis are still unknown.

In this study, a BCAA-enriched or a commercially available amino acid-glucose solution was infused into rats having acute liver injury and liver cirrhosis to evaluate the nutrition of the two solutions and the best route for administering them. As it is important to manage the nutrition of patients such that hepatic encephalopathy is not induced, the effect of a preadministration of the BCAA-enriched solution on ammonia-induced encephalopathy was also studied. In prior infusion experiments with rats, the daily infusion volume, number of calories and amino acid dose were 50-100 ml, 40-80 kcal and 2-4 g, respectively (20), but in this study only 48 ml, 40 kcal and 2 g so as to prevent secondary liver injury due to over loading (21). Since the daily intake of water, calories and protein by an adult rats is approximately 40 ml, 54 kcal and 3 g, respectively (22), the administrations in these experiments were within a reasonable range.

Since amino acids promote the synthesis of protein and DNA in the liver, the

administration of amino acids as a nitrogen source is indispensable. However, application of the commercially available amino acid solution in the nutrition management of severe liver disease could further impair abnormal nitrogen metabolism, including ammonia and amino acid metabolism, and possibly induce hepatic encephalopathy. Therefore, mainly a glucose solution has been used for severe liver disease in the past. It has been recently discovered that the administration of a BCAA-enriched solution to patients with hepatic encephalopathy can induce recovery from hepatic encephalopathy and normalize an abnormal plasma aminogram; thus, the application to nutrition of BCAA is considered to be important (23). BCAA are supposed to be essential amino acids which stimulate the synthesis of albumin in the liver and suppress protein catabolism (24).

Comparative studies of ED and TPN have been previously conducted regarding the effects on nutrition and on the secretion of hormones and digestive juice. ED and TPN have been applied mostly to patients having had a gastrectomy or with the short-gut syndrome, and both methods similarly maintain and improve the general condition (25). TPN inhibits pancreatic secretion (27). The nutrients in ED are directly absorbed from the intestinal tract, and, therefore, ED dose not affect the secretion of digestive juice very much (28). It is well known that the long-term application of TPN induces shortness of the microvilli of the rat's jejumum (29). Since ED scarcely affects these changes, ED is superior to TPN in terms of nutrition management. However, no comparative study of ED and TPN has been done with liver disease patients.

The simultaneous preadministration of amino acids and glucose is effective in preventing the occurrence of acute liver injury. Rats receiving the commercially available amino acid solution prior to CCl_4 treatment revealed higher blood ammonia levels than those receiving the BCAA-enriched solution. Therefore, the continuous administration of a large dose of the commercially available amino acid solution is undesirable and dangerous to the injured liver. The preinfusion of the BCAA-enriched amino acid-glucose solution prevented similarly acute liver injury due to GalN as that due to CCl_4. However, infusion of glucose alone had no such effect. Since liver injury caused by liver toxins such as CCl_4 and GalN was suppressed by the preadministration of the BCAA-enriched amino acid-glucose solution, the maintenance of good nutrition may protect against liver injury and prevent the injured liver from further deterioration. Furthermore, the administration of the BCAA-enriched amino acid-glucose solution led to a decrease in serum GPT activity and had a reparative effect on the injured liver. Both of the two amino acid solutions with glucose were much more effective in maintaining body weight and nitrogen balance than glucose or electrolyte alone. It is difficult to prevent the catabolism of body protein by using glucose alone. Infusion of the BCAA-enriched amino acid-glucose solution into the jugular vein of cirrhotic rats increased the blood ammonia levels slightly more than the infusion of either the electrolyte or glucose solution. The enteral administration of the BCAA-enriched

amino acid-glucose solution, however, did not induce such an increase. Furthermore, an increase in blood ammonia was observed following the enteral or intravenous administration of the commercially available amino acid solution and glucose to cirrhotic rats, perhaps because ammonia detoxication was impaired by the increased concentration of methanethiol (an inhibitor of urea cycle) often seen in cirrhotic patients (30). The Hepaplastin value, which is low in cirrhotic rats before the infusion, was maintained at a good level only by using the BCAA-enriched amino acid-glucose solution, which suggests that BCAA are effective in promoting protein synthesis. Nutrition management with the BCAA-enriched amino acid-glucose solution improved ICG clearance, though the simultaneous administration of sugar with the BCAA may be important for this improvement. Sufficient pre-administration of the BCAA-enriched solution to cirrhotic rats prevented the occurrence of ammonia-induced encephalopathy. These results offer support to the use of nutrition management with BCAA for therapy of patients with liver cirrhosis since the results coincide with clinical reports describing the improvement of nitrogen balance, abnormal liver function and impaired protein synthesis without blood ammonia elevation by administering a BCAA-supplemented diet to cirrhotic patients (31). Since BCAA administration results eventually in nitrogen, the administration of branched-chain α-keto acids to severe liver disease patients with abnormal nitrogen metabolism should be studied in the future.

The enteral preinfusion of the BCAA-enriched amino acid-glucose solution is more effective in preventing acute liver injury than the intravenous preinfusion considering the histological findings and changes in the relative liver weight. Furthermore, the enteral administration of the nutrients is more effective in repairing acute liver injury than the intravenous infusion, since the former suppressed serum GPT activity more than the latter. Nutrition management by the enteral route, thus, seems superior in inhibiting acute liver injury and accelerating repair, although from the standpoint of pre-hepatic nutrition, direct absorption of the nutrients through the portal vein is suitable (32). No remarkable difference was observed in nutrition management of the cirrhotic rats treated with either route from the aspects of histology, blood ammonia level, serum GPT activity, secretion of pancreatic hormones and nitrogen balance. Accordingly, enteral and intravenous infusions are almost equal in maintaining the general nutritional condition in liver cirrhosis. In nutrition management of chronic liver disease, a BCAA-supplemented diet and enteral administration of the nutrients through a fine nasogastric tube should be effective in preventing further deterioration of the liver.

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