Promotion of healing by orally administered glutamine in elemental diet after small intestinal injury by X-ray radiation

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Glutamine was administered orally to rats with damaged small intestinal mucosa as the result of injury by X-ray radiation at 10 Gy to the abdomen. The healing effects of glutamine on the injured mucosa were studied serially from the day of radiation (Day 0) to Day 4. The rats received two types of isocaloric elemental diet, Gln(+) containing 2% glutamine and Gln(−) containing no glutamine, by paired feeding.

From Day 2 to Day 4, the wet weight, protein content, and DNA content of the jejunal mucosa were significantly greater in the Gln(+) than in the Gln(−) group. On Day 3, when the damage of the intestinal mucosa was the severest, the crypt cell production rate in the jejunum was significantly higher in the Gln(+) than in the Gln(−) group. The permeability of the intestinal mucosa to ^{51}Cr-EDTA, administered to the rat stomach through an oro-gastric tube, remained significantly lower in the Gln(+) group. Light microscopic findings showed that oedema in the lamina propria mucosae of jejunum and fusion of jejunal villi were milder in the Gln(+) group on Day 4, when the mucosal mass began to recover. The arterial and portal blood glutamine concentration, and glutamine extraction by the gut from arterial blood and phosphate-dependent glutaminase activity in the jejunal mucosa, were higher in the Gln(+) than in the Gln(−) group. Ornithine decarboxylase activity was increased in both the jejunum and the ileum from Day 3, but no difference was observed between the two groups.

These findings suggest that, after X-ray radiation injury of the intestinal mucosa, the oral administration of the elemental diet containing 2% glutamine improved glutamine metabolism of the body, promoted the proliferation of jejunal epithelium, accelerated the recovery of the mucosal mass and the morphology of villi, and then contributed to maintaining the barrier function of the intestine from an early stage after the injury.

Introduction

Glutamine has not been considered important as a component of nutritional preparations, because it is a non-essential amino acid, has a low solubility, and is unstable in aqueous solution forming pyroglutamate and ammonia[1]. Recent studies, however, have disclosed that enterocytes play an important role in metabolism of amino acids, especially glutamine, and glutamine is the primary source of energy for the enterocytes[2-4]. It has also been reported that glutamine requirement increases when the intestinal mucosa is damaged[5,6]. These observations have led to increased attention to glutamine as a nutrient for the intestine with injured or atrophic mucosa[7-10]. Recently, there have been many reports that oral administration of glutamine from a few days before intestinal injury had prophylactic effects[11-13]. There were also some reports that indicated that oral administration of glutamine after injury promoted for the intestinal mucosal repair[14]. After the rat intestinal mucosa had been damaged by X-ray radiation, Klimberg et al.[15] orally administered a preparation containing 3% glutamine as the only amino acid and showed the usefulness of the glutamine by evaluation of the mucosal mass and glutamine metabolism on Day 8. However, there are few studies on the effects of glutamine, orally administered after injury, on the early healing process in injured intestinal mucosa and which considering the amino acids balance.

In this study, therefore, effects of glutamine in the elemental diet administered after injury on the small intestinal repairing process were examined by mucosal mass, crypt cell proliferation, glutaminase activity, and permeability to ^{51}Cr-EDTA.

Furthermore, ornithine decarboxylase (ODC) is a key enzyme for cell proliferation, and its activity is known to increase before cell proliferation[16,17]. The activity of this enzyme, moreover, is reported to increase during the mucosal repair after intestinal damage[18,19]. Thus, the changes of ODC activity in the small intestinal mucosa were also measured serially.

Materials and methods

Wistar male rats, weighing 240–270 g (Clea Japan Co., Tokyo, Japan), were housed in wire-bottom cages and acclimated for at least three days. During this period, the animals were given common food pellets for rats and water ad libitum.

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Experiment 1: Mucosal parameters and blood glutamine concentration

Changes in the intestinal mucosal mass, polyamine synthesis, histological findings, glutaminase activity, and blood glutamine concentration were measured in 66 rats before and after X-ray radiation to the abdomen.

First, 12 rats were divided at random into two groups given a glutamine-free diet (Gln [−] group) and a group given a glutamine-containing diet (Gln [+] group). After an overnight fast, the animals were anaesthetized by intraperitoneal administration of pentobarbital (30 mg/kg body weight) between 10:00 and 12:00, weighed and radiated with X-rays in a single dose of 10 Gy. The rats were fixed in the supine position on the X-ray radiator (MBR-1520R, Hitachi), covered with a lead plate 3 cm in thickness except for the abdomen from the xyphoid process to the pubis (field, 9×6 cm^2), and radiated at a source-skin distance of 50 cm.

The rats were then caged individually and given Gln(−) or Gln(+) diet. The food was given ad libitum, but the daily food intake of the two groups was equalized by paired feeding.

The food was prepared by eliminating or adding glutamine from the elemental diet Elental® (Ajinomoto Co., Tokyo, Japan). In order to equalize the weight of total amino acids of Gln(−) to that of Gln(+), the contents of other amino acids were increased in Gln(−) and were reduced in Gln(+) (Table 1). They were given to the rats after being dissolved at 1 kcal/ml. The glutamine concentration of Gln(+) preparation in the diluted solution was 2.0%.

At night on the day of radiation, the rats were anaesthetized intraperitoneally with pentobarbital, the abdominal wall was incised after body weight measurement, a 21-gauge catheter was inserted into the portal vein and 2–3 ml of the portal blood was collected. Blood was also sampled from the abdominal aorta. These blood samples were deproteinated by adding the same volume of 5% sulfosalicylic acid, and mixing sufficiently, and centrifuged at 30 000 **g** at 4 °C for 15 minutes. The supernatant was stored at −20 °C and assayed later for glutamine by automated high performance liquid chromatography (L-8500, Hitachi, Tokyo, Japan)[20]. Glutamine extraction from artery by the gut was calculated by the following equation[15]:

$$Ext=(A-P)/A \times 100$$

EXT: Gut glutamine extraction (%).
A: Arterial glutamine concentration.
P: Portal glutamine concentration.

Table 1. Composition of diet formulas (mg).

Amino acids		Elental®[a]	Gln(−)[b]	Gln(+)[c]
Gln		2415	0	7500
Ile		803	941	512
Leu		1124	1318	716
Lys		888	1041	566
Met		810	950	516
Phe		1089	1277	696
Thr		654	767	417
Trp		189	222	120
Val		876	1027	558
His		463	543	295
Arg		1163	1363	741
Ala		1124	1318	716
Asp		1823	2137	1161
Gly		631	740	402
Pro		788	924	502
Ser		1449	1699	923
Tyr		138	162	88
Total amino acid	(g)	16.427	16.427	16.427
Dextrin	(g)	79.37	79.37	79.37
Soy bean oil	(g)	0.636	0.636	0.636
Others	(g)	3.567	3.567	3.567
Total	(g)	100.000	100.000	100.000

[a] Clinically used elemental diet.
[b] Gln(−) contained no glutamine. The content of other amino acids was more than that of Elental® and the ratio was 1:1.172.
[c] Gln(+) contained 2% glutamine when it was diluted to 1 kcal/ml solution. Other amino acids were less than that of Elental® (1:0.637).

The rats were then decapitated, the small intestine from Treitz's ligament to the terminal ileum was resected, rinsed with phosphate buffered saline (pH7.6) at 4 °C, and suspended with a 10-g weight. A 10-cm jejunal segment from 5 cm to 15 cm anal from Treitz's ligament and a 10-cm ileal segment from 10 cm to 20 cm oral from the terminal ileum were cut, incised longitudinally on an ice-cooled plate, and the mucosa was scraped with a glass slide. After measurement of the wet weight of the mucosa, it was homogenized at 4 °C for 30 seconds with 10 ml phosphate buffered saline (pH7.2) containing 0.1 mM pyridoxal-5′-phosphate and 5 mM dithiothreitol with an ultra-disperser (LK-22, Yamato Scientific Co., Tokyo, Japan). A part of the homogenate was used for determination of the ODC activity which was measured by the release of $^{14}CO_2$ from L-(1-^{14}C)-ornithine (American Radiolabeled Chemicals Inc., St. Louis, USA)[18], and the other part was mixed with the same volume of 10% trichloroacetic acid, stirred, and centrifuged at 30 000 **g** for 15 minutes, and the supernatant was stored at −70 °C for the assay of polyamines by HPLC[21]. The remaining homogenate was stored at −20 °C for determination of the protein content by the method of Lowry et al.[22] and the DNA content by fluorometric method[23].

Next, 10-cm segments were collected from 15 cm to 25 cm anal from Treitz's ligament and from 20 cm to 30 cm oral from terminal ileum. The mucosa was scraped, homogenized with 5 ml of 125 mM potassium phosphate buffer (pH7.6) containing 330 mM sucrose and 2 mM dithiothreitol by 20 strokes of a motor-driven Teflon-glass homogenizer, and assayed for the phosphate-dependent glutaminase activity[24].

Segments (1 cm) were collected from the jejunal and ileal stumps, immersed with 10% buffered formaldehyde solution, and examined histologically under a light microscope with hematoxylin -eosin stain.

The jejunal and ileal mucosa was collected by the same method from the two groups (n=6 each) on four consecutive days from the day after X-ray radiation (Day 1–4). Sampling was done similarly in six rats on the day before X-ray radiation (Day-1). All samplings were done between 21:00 and 23:00 each day while confirming that the food had arrived at the stomach and the small intestine, to evaluate the effect of oral food intake on the intestinal mucosal ODC activity under the same con-

ditions. Polyamines were assayed in the samples only on the day when ODC activity was elevated.

Experiment 2: Crypt cell production rate (CCPR)

Twenty rats were divided into two groups after X-ray radiation, and were maintained with Gln(−) and Gln(+) diet as in Experiment 1. On Day 3, the animals were anaesthetized with diethylether, injected intraperitoneally with vincristine sulfate (Shionogi Pharmaceutical Inc., Osaka, Japan) at 1.0 mg/kg body weight, and two animals in each group were killed by decapitation after 30, 50, 70, 90, and 110 minutes. Jejunal and ileal segments were collected from the same sites as in Experiment 1, and were immersed in Carnoy's fixing fluid. These samples were stained with Schiff's reagent, crypts were cut one by one under a stereoscopic microscope, and ten crypts in each intestinal segment were picked up. The number of metaphase cells per crypt was counted under a light microscope, and CCPR was calculated[25].

Experiment 3: Intestinal permeability

Twelve rats were divided into two groups after X-ray radiation, and were fed with Gln(−) or Gln(+) diet. On Day 3, the animals were anaesthetized with diethylether, and 2 ml of physiologic saline containing 37 kBq ^{51}Cr-EDTA (NEN Research Product Co., Boston, USA) was infused into the rat stomach through an oro-gastric tube. The rats were thereafter housed individually in metabolic cages, being allowed to have free access to water. The radioactivity in the urine pooled for six hours was counted with a gamma counter, and the permeability of the intestine to ^{51}Cr-EDTA was calculated[26].

Statistical analysis

The statistical analyses were made using the Stat Flex statistical program (Nankodo Co., Tokyo, Japan). The data were expressed as the means±SEM and compared between the two groups by *t*-test at the significance level of $P<0.05$.

Result

Experiment 1: Muscosal parameters and blood glutamine concentration

All rats survived after X-ray radiation. The food intake of the rats was 12–38 ml/rat/day (the mean±SEM for 4 days was 23.8±3.3 ml/rat/day) and was lowest during Day 2–3 (Table 2). No significant difference was observed in body weight changes between the Gln(−) and the Gln(+) groups.

The wet weight of the mucosa was lowest on Day 3 in the jejunum and ileum in both groups and tended to recover on Day 4. It was significantly higher in the Gln(+) than in the Gln(−) group in the jejunum on Day 2, 3, and 4. Changes in the protein content were similar to those of the wet weight of the mucosa and were significantly higher in the Gln(+) than in the Gln(−) group in the jejunum on Day 2,3, and 4. The DNA content also showed similar changes (Figs 1 and 2).

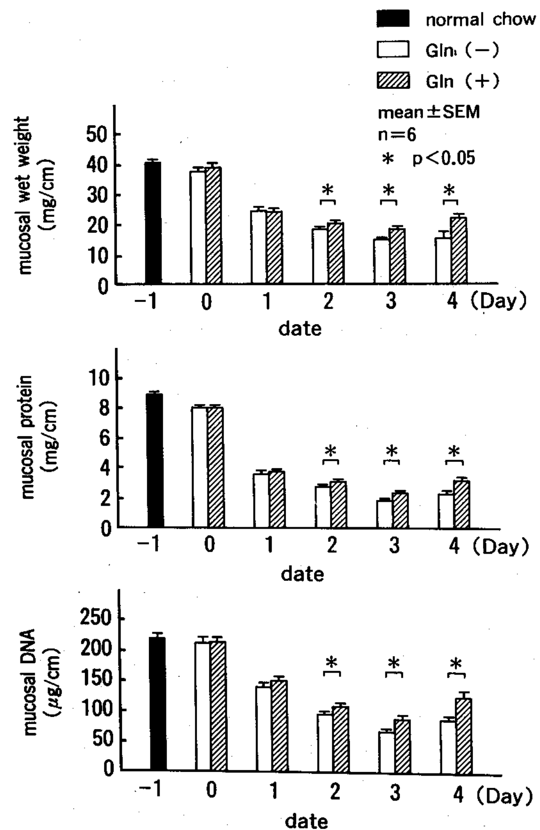

Fig. 1. Wet weight, protein content, and DNA content in the jejunal mucosa. X-ray radiation was performed on Day 0.

By light microscopy on Day 4, when the damaged mucosa began to recover, the jejunum in the Gln(−) group showed marked oedema and inflammatory cell infiltration in the lamina propria mucosae, marked fusion of villi, and severe morphological abnormalities (Fig. 3). Such changes were present but milder in the Gln(+) group (Fig. 4). The morphological differences between two groups were also shown in the jejunum on Day 2 and 3, but they were not so remarkable as those on Day 4.

Table 2. Oral intake and body weight change.

	Oral intake[a]					
Date	Day −1~0	0~1	1~2	2~3	3~4	Day 0~4
Intake(ml/day/rat)	Starved	38±5	27±3	12±3	18±3	23.8±3.3
	Body weight change from Day −1[b]					
Date	Day 0	1	2	3	4	
Gln(−) (g)	−5±1	−19±1	−36±2	−58±2	−71±2	
Gln(+) (g)	−8±1	−21±1	−35±2	−52±3	−64±2	

[a] Measurement of six pairs of rats killed on Day 4 (mean±SEM).
[b] Measurement of six rats in each fed group killed on Day 4 (mean±SEM).

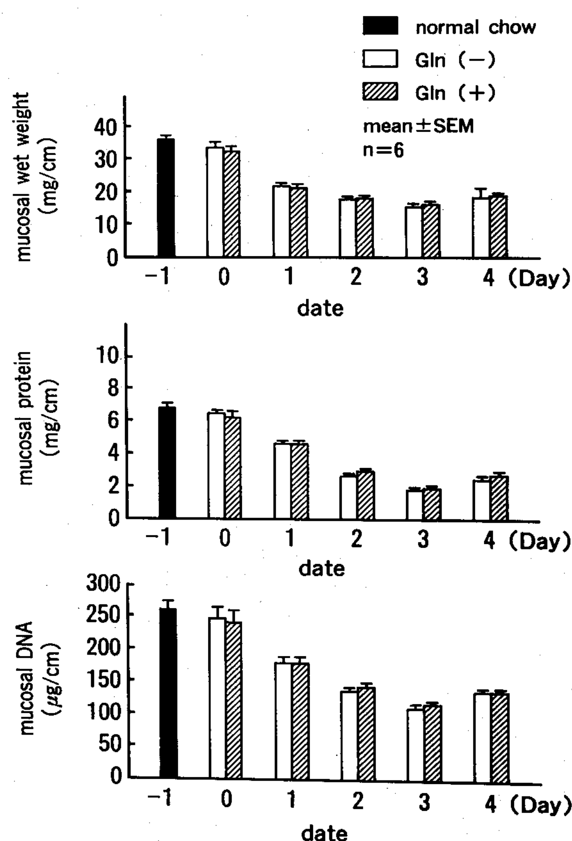

Fig. 2. Wet weight, protein content, and DNA content in the ileal mucosa.

The phosphate-dependent glutaminase activity in the intestinal mucosa was increased in the jejunum on Day 0 and Day 1 in both groups, suggesting the increased glutamine utilization, but it was significantly higher in the Gln(+) than in the Gln(−) group. In the ileum, the activity increased from Day 1 and became higher in the Gln(+) than in the Gln(−) group on Day 2 (Fig. 5).

The arterial glutamine concentration was significantly higher in the Gln(+) than in the Gln(−) group from Day 0 to Day 4 except Day 1. In the portal blood, the glutamine concentration was significantly higher in the Gln(+) than in the Gln(−) group on Day 0 and 1. The glutamine extraction in the intestine was significantly higher in the Gln(+) than in the Gln(−) group on Day 2 and 3 (Fig. 6).

The ODC activity increased in both the jejunum and ileum after Day 3, but no significant difference was observed between the two groups (Fig. 7).

Mucosal polyamine levels were determined in the jejunum using samples on Day 3. No significant difference was observed in the putrescine, spermidine, or spermine levels between the two groups (Table 3).

Table 3. Polyamine content in the jejunal mucosa on Day 3 (n mol/g protein).

	Putrescine	Spermidine	Spermine
Gln (−)	849±51	5324±632	2379±266
Gln (+)	654±66	5034±587	2273±278

Mean±SEM, n=6. There were no significant differences between Gln(−) and Gln(+).

Experiment 2: CCPR

In the jejunum, CCPR was significantly higher in the Gln(+) than in the Gln(−) group on Day 3, 22.8±0.9 vs 14.4±0.4 cells produced /crypt/h (mean±SEM, n=20 crypts, P<0.05), suggesting that crypt cell proliferation was promoted by glutamine in the jejunum. No significant difference was observed between the two groups in the ileum, ie 20.6±0.9 vs 16.9±0.8.

Experiment 3: Intestinal permeability

The permeability of the intestine to ^{51}Cr-EDTA was significantly lower in the Gln(+) than in the Gln(−) group on Day 3, ie 3.5±0.9 vs 9.5±1.8 % (mean±SEM, n=6, P<0.05), suggesting that the glutamine administration kept the permeability of the intestinal mucosa low even under the conditions of the severest atrophy of the intestinal mucosa.

Discussion

In many earlier studies on the effects of oral glutamine administration on injured intestinal mucosa, glutamine was replaced with glycine in food given to animals of the control group. In this study, however, we avoided replacing glutamine with glycine, which has a strong ODC-inducing activity in the normal small intestine[27,28], because we also intended to study the ODC activity. Animals were fed food obtained by modifying the composition of Elental®, a clinically used elemental diet, without changing the total amino acids contents or increasing the contents of particular amino acids other than glutamine. In our preliminary study, the repairing effect of the elemental diet containing 0.6% (Elental®) and 1.0% glutamine on injured intestinal mucosa was not so remarkable, and so, the diet containing 2% glutamine was used in this study.

In our preliminary examinations, the repairing effect of oral glutamine on mildly injured intestinal mucosa by low dose radiation at 2.5 Gy or 5.0 Gy had not been remarkable, and on the other hand, the rats had died from Day 1 to Day 3 by high dose radiation at 12.5 Gy or 15 Gy. Therefore, we settled the dose as 10 Gy.

Since the food was orally ingested by the rats, the oral glutamine intake was decreased after X-ray radiation, so that it might have not been sufficient to prevent degradation of muscle protein and body weight losses associated with the release of endogenous glutamine induced by injury of the intestine. However, the Gln(+) diet had nutritional effects on the intestinal mucosa. The differences of the mucosal parameters between the Gln(−) and the Gln(+) group suggested that orally administered 2% glutamine promoted repair of the jejunal mucosa. It was also recognized because glutamine administration was started after the injury that the differences were not due to prophylactic effect of glutamine but a repairing effect by cell proliferation. This effect was observed from Day 2, when the mucosa was damaged severely, to Day 4, when signs of recovery began to appear. It was also confirmed morphologically that glutamine markedly contributed to the repair of the jejunal mucosa on Day 4. Recently, bacterial translocation with injured mucosa of small and large intestine or with the mucosal atrophy by total parenteral nutrition has attracted attention[11,29]. The degree of bacterial translocation is not seemed to

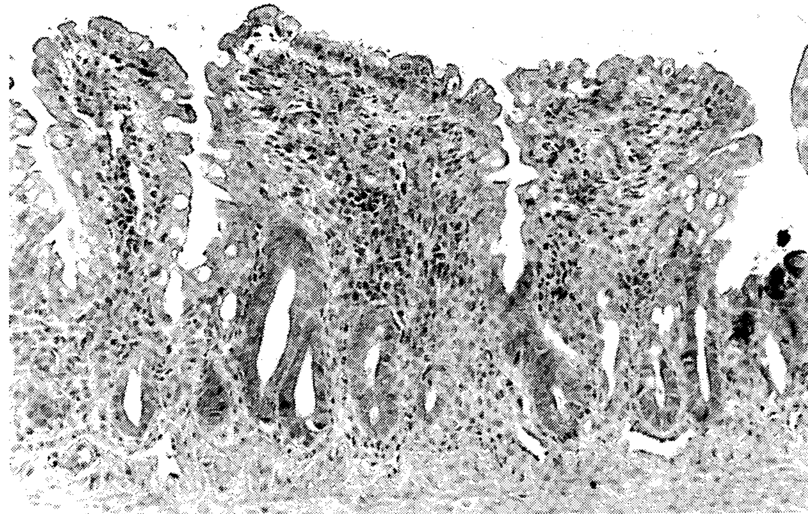

Fig. 3. Light microscopic section of jejunum from Gln(−) rat on Day 4 (haematoxylin-eosin stain, original magnification × 200). Marked oedema and inflammatory cell infiltration in the lamina propria mucosae, and marked fusion and deformity of the villi, are shown.

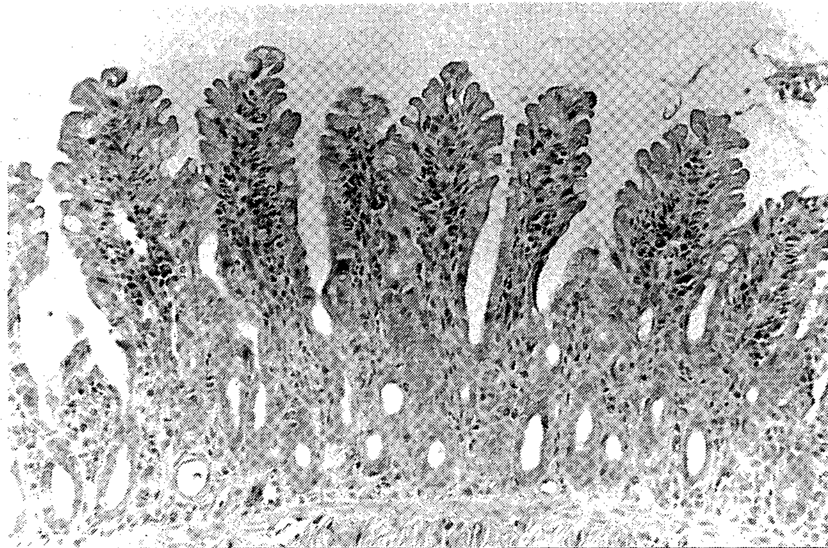

Fig. 4. Light microscopic section of jejunum from Gln(+) rat on Day 4 (haematoxylin-eosin stain, original manification × 200). Oedema, inflammatory cell infiltration in the lamina propria mucosae, and fusion and deformity of villi are milder than those of Gln(−).

parallel with that of the permeability to ^{51}Cr-EDTA with a molecular weight of 358. However, the permeability to ^{51}Cr-EDTA is considered to reflect an aspect of the barrier function of the intestinal mucosa and it is also useful to evaluate the active stage of inflammatory bowel disease[30]. In this study, the difference of the permeability between the two groups indicated the usefulness of glutamine to prevent the intestinal barrier function from the destruction. In addition, the increased CCPR on Day 3 suggested that proliferation of crypt cell and regeneration of the villous epithelium in the jejunum were promoted by glutamine from the early stage when the damage of the intestinal mucosa was severest.

Since arterial and portal blood flow were not measured in this study, the true quantity of the glutamine extracted by the gut was unknown. But the degrees of the extraction could be comparable between the two groups[4,15]. The data of arterial glutamine concentration and glutamine extraction showed that glutamine supply from the blood as the fuel for the intestinal repair was increased in the Gln(+) by comparison with the Gln(−) group. The activity of phosphate-dependent glutaminase, which is the major enzyme involved in the metabolism of glutamine, increased in the jejunum from Day 0 (12 hours after X-ray radiation and about four hours after the beginning of oral ingestion of the food), suggesting that glutamine was utilized in the jejunal mucosa from a very early stage after injury. However, in

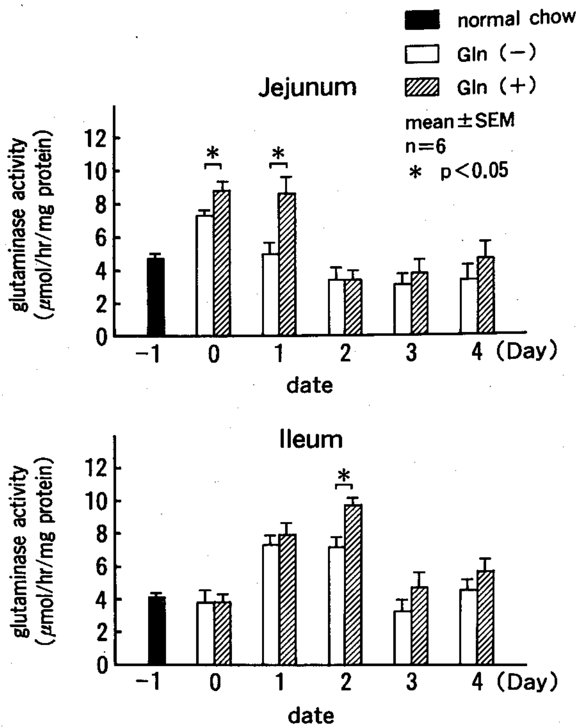

Fig. 5. Phosphate-dependent glutaminase activities in the jejunal and ileal mucosa.

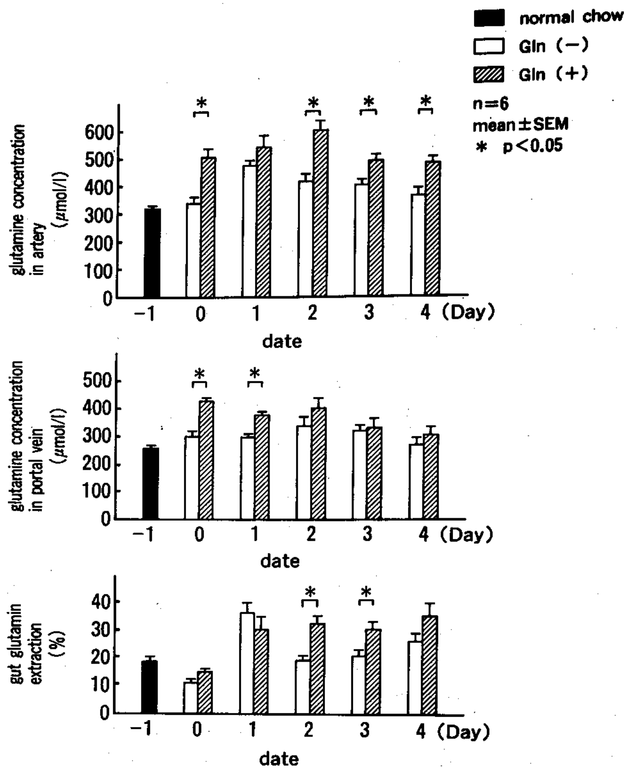

Fig. 6. Glutamine concentration in artery and portal vein, and gut glutamine extraction. Gut glutamine extraction (Ext) was calculated by following equation:
Ext = (arterial Gln−portal Gln)/arterial Gln×100.

spite of a high percentage of gut glutamine extraction of the Gln(+) group on Day 2 and Day 3, the dates when the glutaminase showed higher activities in the Gln(+) group were Day 0 and Day 1. There was a time gap between the changes of the glutamine extraction and jejunal glutaminase activity. Moreover, the glutaminase

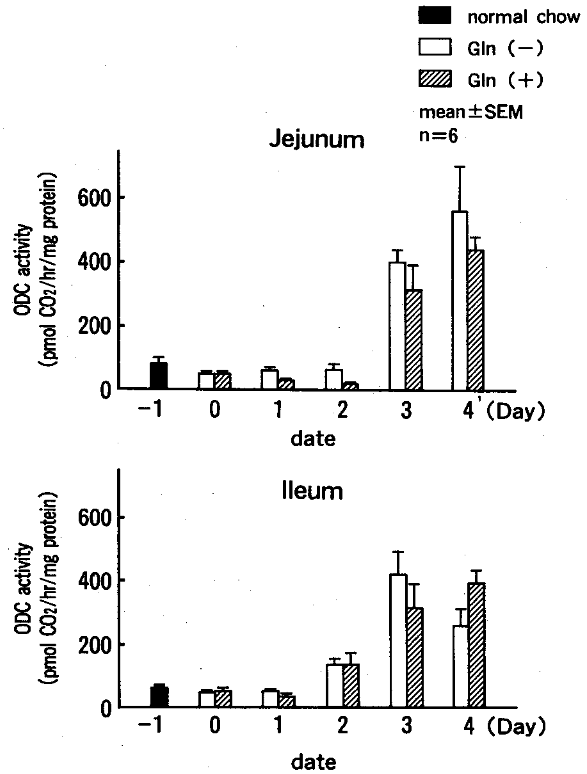

Fig. 7. Ornithine decarboxylase (ODC) activities in the jejunal and ileal mucosa.

in the ileum also showed high activity in the Gln(+) than in the Gln(−) group. If the arterial blood was the primary source of glutamine, there would be no time gap, and if so, the repair in the Gln(+) group might have also been promoted in the ileum, where glutaminase activity was increased, however a healing effect was notable only in the jejunum. It may be inferred from these observations that orally administered glutamine produced a repairing effect by directly acting on the intestinal epithelium in addition to the blood glutamine supply, from a very early stage after the injury, the effect being notable in the jejunum because glutamine concentration was higher in the jejunal lumen than in the ileal lumen. A study involving glutamine infusion through an ileal fistula may be needed to confirm this hypothesis.

The ODC activity increased after Day 3, suggesting cell proliferation in crypts. However, there was no significant difference between the Gln(−) and the Gln(+) groups or between the jejunum and the ileum. In the jejunum, polyamines levels were not different between the Gln(−) and the Gln(+) group. Enteral amino acids induce ODC activity in the normal intestine, but the degree of induction differs among the kinds of amino acids. Glutamine is one of those with less ODC-inducing activities[28]. In this study, it was suspected that the changes of ODC activity by glutamine administration were masked by the effect of the other amino acids than glutamine. However, CCPR was significantly increased in the Gln(+) group. This findings indicated that the proliferation of mucosal cells were promoted by oral glutamine administration.

Conclusion

An elemental diet containing 2% glutamine was orally

administered to rats after mucosal injury was induced in the small intestine by abdominal X-ray radiation at 10 Gy and serial changes of the intestinal mucosa were studied. It was shown that radiation injury was milder in the jejunum from Day 2 to Day 4 in the group administered glutamine as the result of the changes in the mucosal parameters, differences in the barrier function of the intestine, and the morphological findings of villi. The effects of glutamine are considered to be due to promotion of mucosal regeneration by utilization of glutamine as gut fuel from an early stage after injury.

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Asia Pacific Journal of Clinical Nutrition 1992; 1:175–182.

摘 要

X 線照射損害小腸後，口服含谷氨醯胺的要素飲食可以促進康復

作者用10Gray(10焦耳/公斤) X 線照射大白鼠腹部，使小腸粘膜損害，然後口服谷胺醯胺，觀察4天内谷氨醯胺對損害粘膜康復的影響。他們給大白鼠配對喂養兩種相同熱量的要素飲食，一種含2%谷氨醯胺，另一種不含谷氨醯胺。

從第2至第4天，谷氨醯胺組空腸粘膜的蛋白質，脱氧核糖核酸和濕重均明顯大於非谷氨醯胺組，在腸粘膜損害最嚴重的第3天，谷氨醯胺組大鼠的空腸腺窩細胞生長率明顯高於非谷胺醯胺組，用胃管經口腔把 ^{31}Cr-EDTA 輸送到大鼠胃中，發現谷氨醯胺組小腸粘膜通透性明顯地下降。第4天當粘膜開始康復時，谷氨醯胺組在光學顯微鏡下可見空腸粘膜固有層水腫和空腸絨毛粘連。谷氨醯胺組的動脈和門靜脈血液谷氨醯胺濃度，腸道從動脈血中吸取谷氨醯胺和空腸粘膜中依賴磷酸的谷氨醯胺酶活性均比非谷氨醯胺組爲高。從第3天起空腸的鳥氨酸脱羧酶活性增加，但兩組大鼠沒有區別。這些發現提出了X 線照射後損害的腸粘膜，口服含2%谷氨醯胺的要素飲食可改善機體谷氨醯胺的新陳代謝，可促進空腸上皮細胞的增生，加速粘膜和絨毛形態學的康復，有助於維持腸道損害早期的屏障功能。