Original Article

# Effects of continuous enteral L-Arginine in a rat model of the short bowel syndrome

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The objective of this study was to evaluate whether continuous enteral supplementation of L-arginine can stimulate intestinal adaptation in a rat model of short bowel syndrome (SBS). Male Sprague-Dawley rats were randomly divided into three groups of 10 each: Sham rats underwent bowel transaction and received continuous enteral nutrition (Control group, Con group), SBS rats underwent 75% small bowel resection and received continuous enteral nutrition (SB group), and SBS rats underwent 75% bowel resection and received continuous enteral nutrition supplemented with L-arginine (300mg/Kg/d) (SB-Arg group). Fat absorbability, plasma free fatty acids, parameters of intestinal adaptation, enterocyte proliferation and apoptosis were determined on day 15 after operation. After massive small bowel resection, rats had significant bowel adaptation. Compared with SB untreated rats, SB rats supplemented with L-arginine demonstrated a significant increase in fat absorbability, plasma level of free fatty acids, ileal mucosal weight and DNA content, jejunal and ileal mucosal protein content, jejunal and ileal villus length, crypt depth and mucosal thickness. L-arginine supplementation increased enterocyte proliferation, while decreasing enterocyte apoptosis. We suggest that after massive small bowel resection, continuous enteral supplementation of L-arginine can stimulate intestinal adaptation. L-arginine may be a trophic factor to stimulate intestinal adaptation in rats of SBS.

**Key Words: short bowel syndrome, adaptation, intestine, L-arginine, enteral nutrition**

## INTRODUCTION

After massive small bowel resection, patients will develop short bowel syndrome (SBS), which is characterized by diarrhea, dehydration, electrolyte disturbances, malabsorption, and progressive malnutrition.[1, 2] Despite a marked improvement in critical care and progress in long-term nutritional support, mortality and morbidity of SBS patients still remain high.[3] The most important factor contributing to patients' outcome is the adaptation capacity of remanent intestine.[4] A variety of agents have been identified as having trophic effects on bowel mucosa and intestinal adaptation, including nutrients and other luminal constituents, gastrointestinal secretions, hormones and peptide growth factors.[5-7]

Arginine is a nonessential amino acid processed metabolically by the urea cycle. L-arginine is converted to nitric oxide (NO) and citrulline by the enzyme nitric oxide synthase. NO is an important molecule involved in neurotransmission, vascular homeostasis, immune regulation, and host defense.[8] Recently, the small bowel has been considered an important organ for the synthesis of citrulline as a precursor of arginine.[9] After small-bowel resection, the role of arginine is a subject of controversy. Arginine becomes an essential amino acid because of a reduction in arginine synthesis in the kidney in the rat model of SBS.[10] Hayrettin *et al* have shown that intraperitoneal injection of L-arginine treatment increased villus height and crypt-cell mitoses after massive small bowel resection.[11] However, Igor Sukhotnik *et al* recently demonstrated that parenteral arginine supplementation in rats with SBS inhibited structural intestinal adaptation.

In this study, we evaluated the effects of continuous enteral supplemental L-arginine on intestinal adaptation in a rat model of SBS.[12]

## MATERIALS AND METHODS

### *Animal and experimental design*

The animal facilities and research protocols were approved by Nanjing University Institutional Animal Care and Use Committee. Thirty male Sprague-Dawley rats weighing 150 to 170 g were housed under standardized conditions (12h light-dark cycle, controlled room temperature) for 5–7 days. Following an overnight fast, the animals were divided into three groups of 10 rats each. Animals were anesthetized with an intraperitoneal injection of ketamine (100 mg/kg). The abdomen was opened through a midline incision. For the rats of SB group and SB-Arg group, the proximal small bowel was resected from a point 5 cm distal to the ligament of Treitz to a point 10 cm proximal to the ileocecal junction.

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The proximal jejunum was anastomosed to the remaining ileum in continuity using interrupted 6-0 silk. Animals of Con group underwent bowel transection and reanastomosis 5 cm distal to the ligament of Treitz. A plastic tube 1.4 cm in diameter was inserted into the stomach by gastrostomy and tunneled subcutaneously, and the dorsal cervical region exited through a spring-swivel apparatus. Water, but not rat chow, was available after the operation. From postoperative day 2 to 14, animals of all three groups received enteral nutrition with 250Kcal/Kg/d calorie intake and 1.45g/Kg/d nitrogen intake, except that on the second postoperative day the nutrition intake was a quarter of the whole amount and on the third postoperative day was half. The nutrient was commercially available Peptide-2000 (Nutricia Ltd, Wuxi, China) containing 16% peptides, 9% fat and 75% glucose. Enteral nutrition was fed continuously for 24 hours with an infusion pump. In SB-Arg group, L-arginine (Sigma-Aldrich, StLouis, MO) was supplemented in the nutrient at a dose of 300mg/kg/d. The weight of the animals was recorded daily. The rats were anesthetized and killed by exsanguination on the 15$^{th}$ postoperative day.

***Measurement of fat absorbability and plasma free fatty acids***

Rat stool from postoperative day 12 to 14 was collected and fecal lipid was extracted using ethanol and petroleum ether as described by Henry.[13] Fat intake was calculated from the amount of enteral nutrition. The difference between the total milligrams of fat intake and the total milligrams of fat remaining in the dry feces represented fat absorbability as previously described by other investigators.[14] In order to further show fat absorbability, plasma free fatty acids were measured by gas chromatography.[15]

***Intestinal composition***

The small intestine from the Treitz ligament to the ileocecal valve was removed and divided at the anastomosis. Portions of the intestine 1 cm on either side of the anastomosis were discarded because of the surgically-induced hyperplasia occurring in the perianastomotic region. The intestine was split on the antimesenteric border, washed with cold saline, and dried, and each segment was weighed. The mucosa was scraped from the underlying tissue with a glass slide and was weighted. Mucosal samples were homogenized with TRIzol reagent (Invitrogen Corp., Carlsbad, CA). DNA and protein were extracted using the method of Chomczynski [16] and were expressed as micrograms per centimeter of bowel per 100 g body weight.

***Histopathological examination***

Intestinal samples from the proximal jejunum and distal ileum were fixed in 10% formalin, dehydrated in progressive concentrations of ethanol, cleared in xylene, and embedded in paraffin wax. Deparaffinized 5-μm sections were stained with hematoxylin and eosin. Villus height, crypt depth and mucosal thickness were measured using a graded eye piece at 10-times magnification by a pathologist blinded as to the tissue origin.

***Measurement of enterocyte proliferation and apoptosis***

Portions of the proximal jejunum and distal ileum were taken as described above. Crypt cell proliferation was assessed using an immunohistochemical technique based on proliferating cell nuclear antigen (PCNA). [17] An index of proliferation was determined as the average number of positive cells from the crypt of Lieberkuhn.

Additional 5-μm thick sections were prepared to establish the degree of enterocyte apoptosis. The TUNEL assay for apoptotic cell detection was performed using the In Situ Cell Death Detection kit (Boehringer Mannheim, Germany).[18] The apoptotic index (AI) was defined as the number of apoptotic TUNEL-positive cells per 1000 cells.

***Statistical analysis***

The data are expressed as mean ± SEM. Statistical analysis of parameters of adaptation, enterocyte proliferation, and apoptosis was performed using the nonparametric Kruskal–Wallis ANOVA test followed by the corrected Mann–Whitney test, with $p<0.05$ considered statistically significant.

## RESULTS

***Body weight changes***

All animals undergoing small bowel resection had diarrhea and weight loss during the first three postoperative days. The SB-untreated rats grew slower than sham animals from days 2 to 14 and had significantly lower final body weights. No final body weight difference was found between SB-Arg group and Con group (Fig 1).

***Fat absorbability and plasma free fatty acids levels***

Rats with massive bowel resection had decreased fat absorbability, suggesting generalized malabsorption. Compared with SB group, rats in SBS-Arg group had higher fat absorbability. Similar results were found in plasma total free fatty acids levels and plasma essential fatty acids levels. (Table 1)

**Table 1**. Effect of bowel resection and enteral arginine on fat absorbability and plasma free fatty acids levels

| | fat absorbability (%) | plasma total free fatty acids (mg/L) | plasma essential fatty acids (mg/L) |
|---|---|---|---|
| Con group | 91.7±3.3 | 702±166 | 380±130 |
| SB group | 81.3±3.9* | 209±77* | 144±67* |
| SB-Arg group | 84.9±3.2*† | 650±87† | 284±56† |

* $p<0.05$ vs. Con group; †$p<0.05$ vs. SB group.

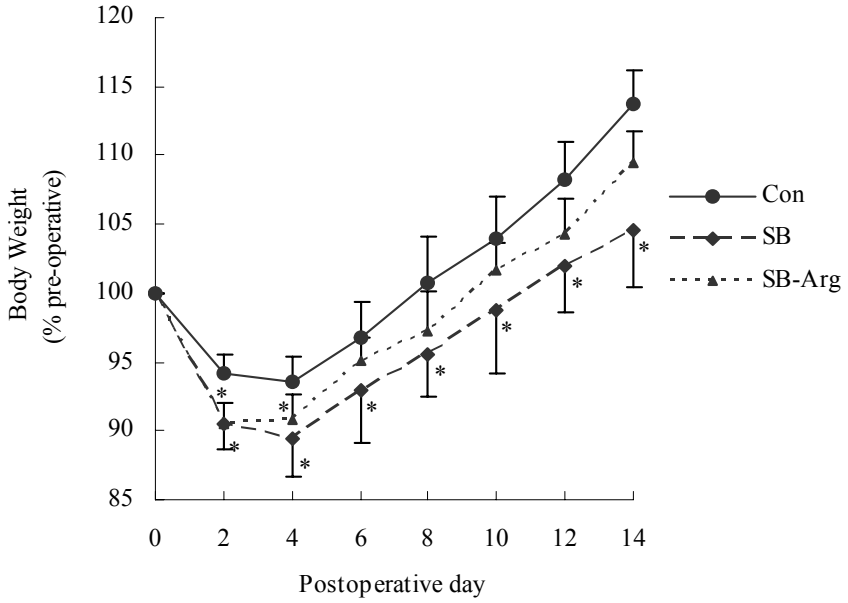


**Figure 1.** Body weight changes in control (*Con*) and untreated resected rats (*SB*) or SBS rats treated with enteral arginine (*SB-Arg*). Values are mean ± SEM. *$p$<0.05 vs. Con group

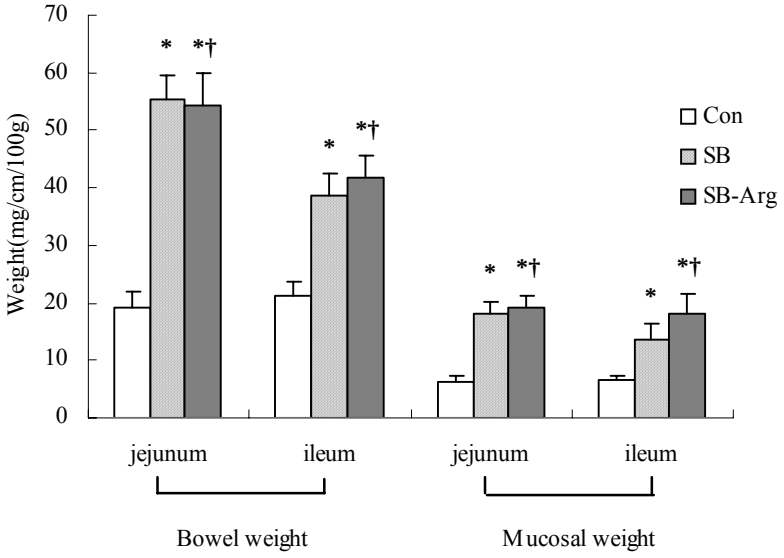


**Figure 2.** Effect of bowel resection and enteral arginine on bowel and mucosal weights in jejunum and ileum. *$p$<0.05 vs. Con group, †$p$<0.05 VS. SB group

***Parameters of intestinal adaptation***

Adaptation in the residual bowel in the resected rats was manifested by a significant increase in bowel and mucosal weight (Fig 2), mucosal DNA and protein (Fig 3), villus height, crypt depth and mucosal thickness (Fig 4). Compared with SBS-untreated animals, SBS rats treated with enteral L-arginine demonstrated a significant increase in ileal mucosal weight (18.0±3.5 vs. 13.5±3.0 mg/cm/100g, $p$<0.05), mucosal DNA content in jejunum (33.5±3.7 vs. 30.2±3.6 μg/cm/100 g, $p$<0.05) and ileum (29.6±3.3 vs. 26.0±2.6 μg/cm/100 g, $p$<0.05), and protein content in jejunum (65.5±7.3 vs. 59.8±6.2 μg/cm/100g, $p$<0.05) and ileum (39.2±2.3 vs. 35.4±2.3 μg/cm/100g, $p$<0.05), villus height in jejunum (503±56 vs. 446±47 μm, $p$<0.05) and ileum (401±40 vs. 356±29 μm, $p$<0.05), crypt depth in jejunum (184±23 vs. 164±16 μm, $p$<0.05) and ileum (155±17 vs. 136±13μm, $p$<0.05), and mucosal thickness in jejunum (683±39 vs. 616±39μm, $p$<0.05) and ileum (550±49 vs. 487±41μm, $p$<0.05).

***Cellular proliferation and apoptosis***

A significant increase in both enterocyte proliferation and enterocyte apoptosis occurred in rats following massive bowel resection compared with sham animals (Fig 5). SBS rats treated with enteral L-arginine demonstrated a significant increase in cell proliferation index in jejunum (31±4 vs. 22±3/crypt, $p$<0.05) and ileum (32±2 vs. 25±3/crypt, $p$<0.05), and a significant decrease in cell

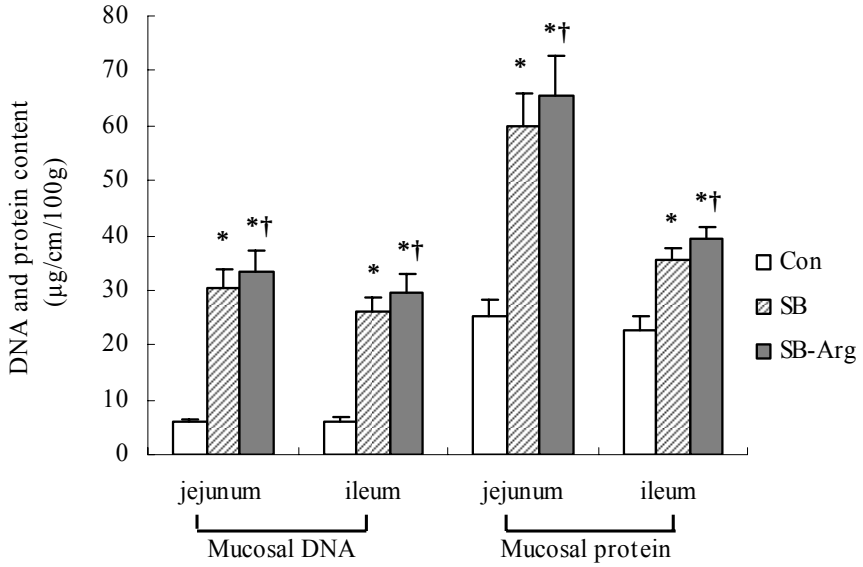


**Figure 3.** Effect of bowel resection and enteral arginine on mucosal DNA and protein content. *$p$<0.05 vs. Con group, †$p$<0.05 vs. SB group

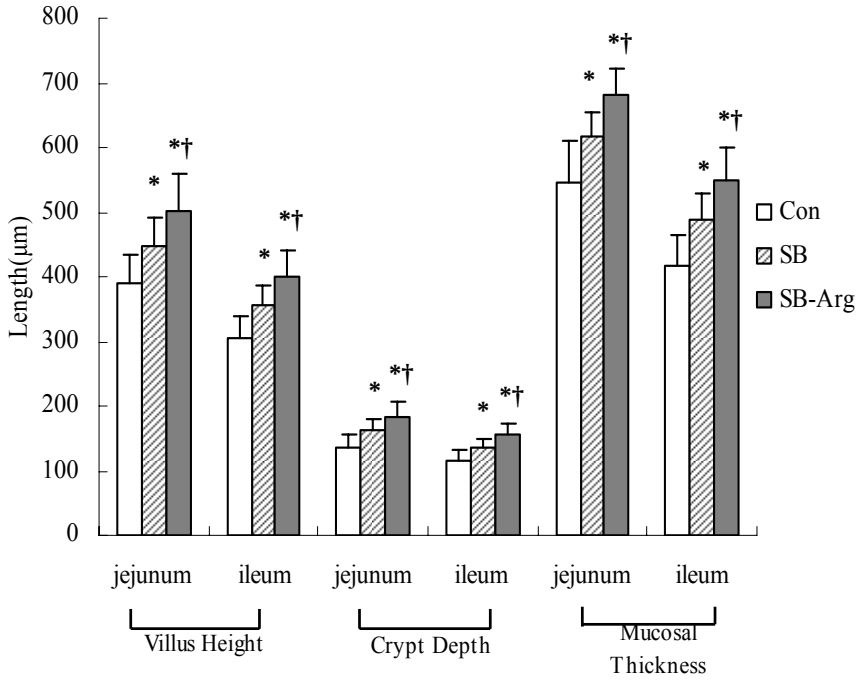


**Figure 4.** Effect of bowel resection and enteral arginine on the microscopic appearance of the remaining small intestine. *$p$<0.05 vs. Con group, †$p$<0.05 vs. SB group

apoptotic index in jejunum (16±3 vs. 22±4/1000 enterocytes, $p$<0.05) compared with SBS-untreated animals.

## DISCUSSION

With the availability of total parenteral nutrition (TPN), advances in resuscitation, availability of potent antibiotics, and modern techniques of organ support, the prognosis of short bowel syndrome has dramatically improved. However, SBS remains a significant cause of infant morbidity and mortality.[3] The key to survival after massive small bowel resection is the ability of the remaining bowel to adapt. Adaptation means progressive recovery from intestinal failure throughout which the small bowel increases its absorptive surface area and its functional capacity in an attempt to meet the body's metabolic and growth needs. [1, 19] In humans, intestinal adaptation begins within 24–48 h of resection and includes morphologic (structural adaptation) and functional changes (functional adaptation) of the residual bowel. Enteral feeding is a major factor in stimulating intestinal adaptation after small bowel resection. Luminal nutrient supply serves as not only an energy source, but also a signal for endogenous secretions and the release of various gut-trophic hormones and growth factors. [1, 20] Long term TPN leads to an inhibition of intestinal adaptation. In recent decades research has focused on identifying numerous factors that stimulate epithelial

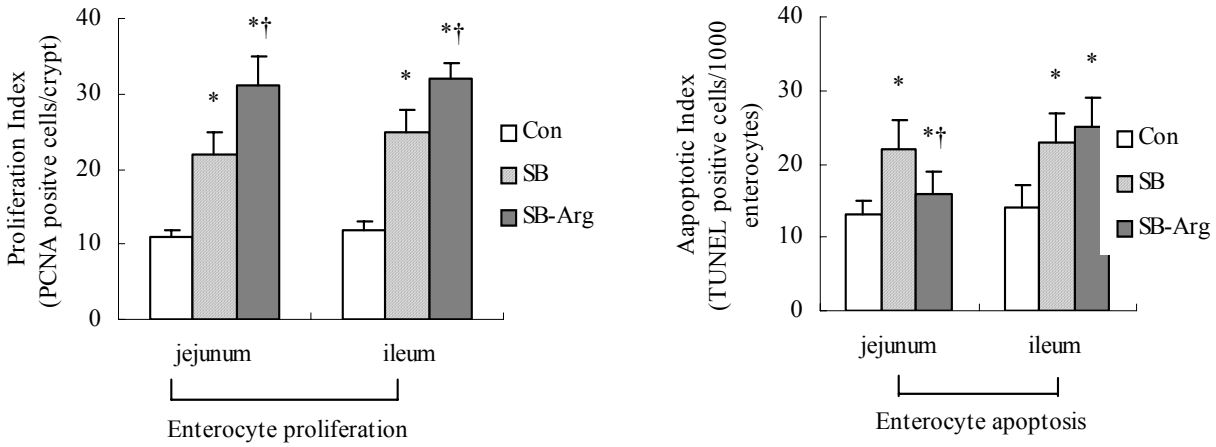


**Figure 5.** Effect of bowel resection and enteral arginine on enterocyte proliferation and enterocyte apoptosis. An index of proliferation was determined as PCNA positive cells from the crypt of Lieberkuhn, and TUNEL assay was used to determine enterocyte apoptosis. *$p$<0.05 vs. Con group, †$p$<0.05 vs. SB group

cell proliferation and differentiation and may potentially have a therapeutic role in treating patients suffering from SBS.[5-7]

Arginine (2-amino-5-guanidinovaleric acid) is classified as a dispensable amino acid for healthy adult humans and as an essential amino acid for young, growing mammals. Arginine has been shown to influence metabolism in mammalian cells directly or through stimulation of the secretion of hormones, such as insulin, growth hormone, glucagon, and prolactin.[21] Also, it has been shown that arginine is required for the synthesis of nitric oxide (NO), polyamines, proline, glutamate, and creatinine.[22] The polyamines putrescine, spermidine and spermine are believed to play an important role in modulating normal and adaptive mucosal growth.[23] L-Arginine is converted to nitric oxide and citrulline by the enzyme nitric oxide synthase (NOS). Arginine and nitric oxide are critical to normal physiology of the gastrointestinal tract. L-Arginine stimulates water and electrolyte absorption by the small intestine.[24] In animal models of intestinal ischemia and sepsis, nitric oxide plays a role in the maintenance of intestinal barrier function.[25] Dietary supplementation with arginine accelerates ulcer healing in experimental ulcerative ileitis and stimulates small intestinal mucosal recovery following experimental radiation enteritis.[26, 27]

There are few and controversial experimental studies concerning the effects of arginine supplementation on intestinal adaptation after massive small bowel resection. The study of Wakabayashi Y *et al* showed that there was arginine deficiency in rats with SBS and that arginine was an essential amino acid after massive small bowel resection.[10] Hayrettin Öztürk *et al* and Alparslanc amli *et al* showed that L-arginine could stimulate intestinal adaptation in rats of SBS.[11] However, not all investigators support this concept. Studies of Igor Sukhotnik *et al* and Carlo F. M. Welters have shown that parenteral arginine supplementation attenuated intestinal adaptation in rats of SBS.[12, 28] The mechanism of L-arginine on intestinal adaptation in SBS is still unclear; however, its production polyamines and nitric oxide may play an important role. Polyamines are involved in the regulation of intestinal mucosal growth after massive bowel resection.[29] Nitric oxide is a small, diffusible, highly reactive molecule with many regulatory roles in physiological and pathological conditions. NO has a beneficial effect on many gastrointestinal disorders. It has been reported previously that at low concentrations, NO may have a protective physiologic function, whereas high NO production may cause intestinal injury, perhaps through the generation of potent radicals.[30] The main physiological signaling pathway of NO is also considered to be the activation or suppression of apoptosis.[31] There is growing evidence suggesting the central importance of apoptosis in controlling the enterocyte mass following massive small bowel resection. Therefore, alteration in enterocyte apoptosis through production of NO may be considered as an additional mechanism by which arginine may affect post-resection bowel growth. Previous studies of the effect of L-arginine supplementation on intestinal adaptation differed both in the administration route, either parenteral route or enteral route, and in administration dose. L-arginine supplementation either by the parenteral route or with high dosage may cause a high concentration of NO, which probably will cause intestinal injury and enterocyte apoptosis. This may partially explain the inconsistent results from different research groups mentioned above.

In the present study, we evaluated the effects of enteral L-arginine supplementation on intestinal adaptation in a rat model of SBS. We used spring-swivel apparatus to provide continuous enteral nutrition. All the rats received the same energy and nitrogen intake according to their body weights. So the possible difference of intestinal adaptation caused by nutrient intake was avoided. Another innovation of this study was that enteral L-arginine supplementation was administered by a continuous pump, which supplied an uninterrupted low dose of L-arginine. In this way, the remnant small intestine would absorb L-arginine more efficiently. The administration dose of L-arginine was 300mg/kg/d, which approached the physiological dosage for rats and might avoid high output production of NO. Our results showed that following massive bowel resection, rats demonstrated increased bowel and mucosal weight, increased mucosal DNA and protein,

lengthening of the villi, and deepening of the crypts, reflecting an adaptive response. Both enterocyte proliferation and enterocyte apoptosis increased in remaining jejunum and ileum. The present study has shown that continuous enteral L-arginine supplement stimulates structural intestinal adaptation following massive small bowel resection in rats. This conclusion is supported by the observed increase in mucosal weight of the remnant bowel, in mucosal DNA and protein, and in villus height and crypt depth in this model. Increased villus height and crypt depth are the results of increased proliferation and accelerated migration along the villus. Increased absorptive surface area is supposed to be accompanied by increased nutrient absorption, so we detected functional adaptation in the present study. Fat absorption of SBS rats supplemented with L-arginine increased significantly, and increased plasma free fatty acids levels also demonstrated the enhanced functional adaptation. Concomitant increases in mucosal DNA and protein content suggest decreased cell metabolism, which is consistent with the increased epithelial cell proliferation and differentiation. This adaptive response was accompanied by an increase in enterocyte proliferation and a decrease in enterocyte loss via apoptosis. Both mechanisms may be responsible for increase in enterocyte mass. The results of the present study add to the body of evidence that supports the beneficial effects of L-arginine on intestinal adaptation following massive small bowel resection.

In summary, in a rat model of SBS, continuous enteral L-arginine administration stimulates intestinal adaptation. L-Arginine may be a trophic factor to stimulate intestinal adaptation in rats of SBS.

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# 持续肠内给予 L–精氨酸对短肠综合征大鼠肠道代偿的影响

本研究目的在于探讨持续肠内给予L-精氨酸对短肠综合征大鼠肠道代偿的影响。雄性Sprague-Dawley大鼠随机分为三组，每组10只。假手术对照组（Con组）行空肠横断吻合，短肠对照组（SB组）和短肠精氨酸组（SB-Arg组）均行75%中段小肠切除。各组大鼠均给予等量的肠内营养支持，其中SB-Arg组肠内营养中添加L-精氨酸300mg/Kg/d。术后第15天检测脂肪吸收率、血浆游离脂肪酸水平、肠道代偿指标、肠粘膜细胞增殖和凋亡。结果显示，大鼠广泛肠切除术后出现明显的肠道代偿。SB-Arg组大鼠脂肪吸收率、血浆游离脂肪酸水平、回肠粘膜重量和DNA含量、空肠及回肠蛋白含量、空肠及回肠绒毛高度、隐窝深度及粘膜厚度均显著高于SB组；添加L-精氨酸能促进短肠大鼠肠粘膜细胞增殖并抑制肠粘膜细胞凋亡。本研究的结果表明，持续肠内给予L-精氨酸能促进短肠综合征大鼠肠道的代偿，精氨酸可能可作为短肠综合征大鼠肠道代偿的一种营养因子。

關鍵字：短腸綜合症、代償、腸道、L-精氨酸、腸道營養。