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World J Gastroenterol 2002;8(1):168-171
World Journal of Gastroenterology
 ISSN 1007-9327

• BASIC RESEARCH •

Preventive effect of glutamine on intestinal barrier dysfunction induced by severe trauma

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Received 2001-06-03 **Accepted** 2001-11-15

Abstract

AIM: **To investigate the mechanism underlying intestinal barrier function damage after severe trauma and the therapeutic effect of glutamine.**

METHODS: **Burned patients, and animal models of severe trauma replicated by hemorrhagic shock combined with endotoxin infusion and burn injury, were included in a serial experiment. Effects of oral glutamine on intestinal barrier function were observed in scalded rats. Parameters measured in these experiments were as follows: plasma levels of diamine oxidase (DAO), tumor necrosis factor (TNFα), endotoxin (LPS), and lactate as well as D-lactate by biochemical methods, lactose/mannitol (L/M) ratio in urine by SP-3400, and pathological examination of intestinal mucosa under light microscopy.**

RESULTS: **Plasma DAO activity was significantly increased after injury. There was a negative correlation between plasma DAO and intestinal mucosal DAO or pHi (r=-0.93, plasma 0.80±0.93,2.83±1.71,1.14±0.64,2.36±2.06 and 2.49±1.67 *vs* intestinal 0.52±0.12,0.34±0.03, 0.45±0.18,0.37±0.26 and 0.41±0.07; r=-0.533, plasma 0.87±0.75,1.89±1.13,1.21±0.23,3.03±2.61 and 4.70±1.22 *vs* pHi 7.03±0.05,7.05±0.06,7.14±0.096, 7.20±0.08 and 7.05±0.07; P<0.01-0.05). Positive correlations were found between DAO activity and plasma TNFα, LPS,, lactate, L/M and D-lactate (r=0.817, 0.842, 0.872, and 0.951; plasma DAO 0.87±0.75, 1.89±1.13,1.21±0.23,3.03±2.61 and 4.70±1.22 *vs* TNFα 0.08±0.02,0.03±0.25,0.17±0.09,0.34±0.15 and 0.33±0.18; *vs* LPS 0.14±0.03,0.16±0.04,0.21±0.02, 0.18±0.16 and 0.37±0.10; *vs* lactate 9.03±2.19, 18.30±2.56,9.81±2.83,12.01±6.83,12.01±6.84 and 43.61±11.27; *vs* L/M 0.03±0.01,0.41±0.27,0.62±0.20, 1.70±0.60; r=0.774, plasma DAO 1.25±0.41,2.17±0.71, 2.29±0.87,1.23±0.55 and 1.11±0.47 *vs* D-lactate 8.37±2.48,18.25±6.18,13.96±4.94,8.93±3.00 and 12.39±4.94;all P<0.01), repestively. Damage of intestinal mucosa was found by pathological examination. Intestinal barrier function was improved to a certain extent by oral glutamine in scalded rats.**

CONCLUSION: **Intestinal barrier function was damaged in the early stage after trauma. Plasma DAO activity, D-lactate content, intestinal pHi and urine L/M may be sensitive markers of intestinal mechanical injury, and glutamine may protect against intestinal barrier dysfunction after severe trauma.**

Li JY, Lu Y, Hu S, Sun D, Yao YM. Preventive effect of glutamine on intestinal barrier dysfunction induced by severe trauma. *World J Gastroenterol* 2002;8(1):168-171

INTRODCTION

It is generally accepted that the intestine may serve as an important organ in the development of severe complications under critically ill conditions, including trauma, burns, shock, etc.[1-3] Hemorrhagic shock and/or gut ischemia-reperfusion injury commonly occur in the early stage after acute insults, leading to gut-derived sepsis as a result of gut barrier dysfunction[4-10]. In order to investigate the mechanism underlying intestinal barrier function damage and its potential interventional measures, burned patients and animal models of severe trauma were employed in our current experiments[6,11-15].

MATERIALS AND METHODS

Animal models

Animal models of severe trauma were replicated by hemorrhagic shock combined with endotoxin infusion. Male Wistar rats, weighing 190g-230g, were anaesthetized with intraperitoneal injection of 30g·L^{-1} barbitone sodium (35mg·kg^{-1}), and the femoral artery and jugular vein were cannulated under aseptic conditions. The rats were then bled via the jugular vein catheter until a mean arterial pressure of 30-35 mmHg (4.6 kPa) was reached. At the end of shock, endotoxin (*E.coli*O55 B5, Sigma) was infused through tail vein at a dose of 2mg·kg^{1}. A goat model of hemorrhagic shock combined with endotoxin challenge was established according to the previous report(n=20)[5]. Animals received *E.coli*O26 B6 endotoxin via portal vein 24h after the recovery from shock, and the dosage was 30 ng·kg^{1}·min^{1}, which was given in a continuous infusion lashing for 5d. Wistar rats were divided randomly into three groups: normal controls, early feeding with standard feed plase Gln 0.5g after scalding, and animals (except control group) sustained a 30% TBSA full-thickness scald covering the back and flanks[6]. Determination of plasma diamine oxidase in 21 burned patients (17 male and 4 female) at the age of 33±10 years, with burn area (64±21)%, and (35±20)% ⅢⅢ0. Plasma DAO activity was determined on day 1, 3, 7, 14 and 21 postburn.Blood and intestinal DAO levels were tested according to our previous report[17]. Plasma lactate and D-lactate concentrations were determined by biochemical methods as described by Brandt *et al*[18]. Microassay for quantitation of endotoxin in blood was made with new PCA treatment using chromogenic limulus amebocyte lysate[19].

Tumor necrosis factor (TNFα) assay. Plasma TNF content was measured by radioimmunoassay.Lactulose/mannitol (L/M) ratio tests in urine were made by SP-3400[20].

Pathological examination. Tissue samples were examined under light microscopy.

Statistical Analyses

Data were expressed as the mean±standard error, and were statistically evaluated by Students t test and correlation analysis. Differences were considered to be significant with P<0.05.

RESULTS

Plasma DAO levels were elevated in double-peak patterns, one at early stage after trauma and another during invading infection in animal models. Similar results were also obtained in burned patients. Meanwhile, intestinal DAO levels were decreased to certain extent after trauma in animal model. There was a significantly negative correlation between plasma and intestinal DAO activity (Table 1; Figures 1 and 2).

Table 1 Changes in plasma DAO in trauma animal model ($\bar{x}\pm s\times10^3$U·L^{-1})

Animal model	Before injury	T (after injury) / h				
		2	6	24	48	72
Goat	0.9±0.8	1.9±1.1[a]		1.2±0.2	3.0±2.6	4.7±1.2[b]
Rats	1.3±0.4	2.2±0.7[b]	2.3±0.87[b]	1.2±0.6	1.1±0.5	
Scalded rats	0.8±0.9	0.8±1.8[b]		1.1±0.6	2.4±2.1[a]	
Burnd pigs	4.1±1.4	4.7±1.5		4.7±1.4	4.8±1.1	5.8±1.4[a]
Gun shooting	1.5±0.6	1.2±0.5	2.0±0.6[b]	1.9±0.2[b]		
Dog in hypothermia						

[a]P<0.05; [b]P<0.01, *vs* before injury.

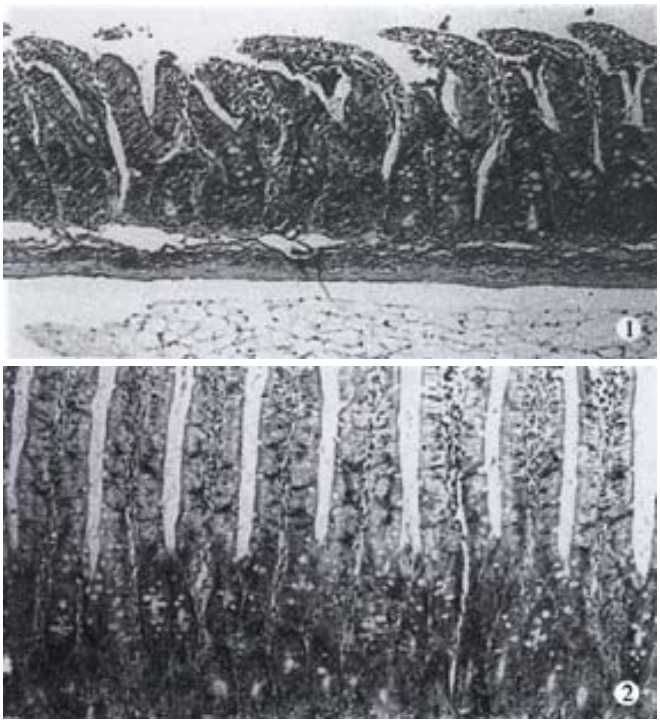

Figure 1 Pathological changes of intestinal mucosa after 8d in scalded rats. HE×100

Figure 2 Pathological changes of intestinal mucosa after 8d oral GLN in scalded rats. HE×100

Plasma DAO concentrations and the level of the related index, and plasma TNFα significantly increased at various intervals after trauma in goats. Plasma endotoxin levels notably increased at 24h and 72h after injury. Blood lactic acid significantly increased from 2h to 72h after trauma. The plasma DAO activity was obviously correlated with plasma TNFα, LPS and lactate (P<0.01; Table 2 and 3). Changes in DAO activity were significantly related with plasma TNFα and LPS levels in scalded rats. Plasma DAO activity and plasmaD-lactate were significantly correlated in rats secondary to hemorrhage followed by endotoxin challenge (r=0.774; P<0.01).

Glutamine could protect against intestinal barrier function damage. The results indicated that plasma DAO activity was decreased in animals with early glutamine supplementation compared with those without glutamine treatment (10h after trauma P<0.05). Results of intestinal pathological examination. The pathologic examination of the intestine showed that the damage of epithelial cells of intestinal mucosa, hemorrhage and necrosis, accompanied by the inflammatory cell infiltration in intestinal wall in goats suffering from hemorrhagic shock combined with endotoxin infusion. It was revealed that there was disruption of intestinal mucosa after scald and gut ischemia-reperfusion combined with endotoxin challenge in rats, whereas oral glutamine supplementation could markedly improve intestinal mucosa following acute insults (Figure 2).

Table 2 Changes in parameters in goats after hemorrhagic shock combined with endotoxin infusion

	Before injury	T (after injury) / h			
		2	24	48	72
TNF / μg·L^{-1}	0.08±0.02	0.03±0.25[a]	0.17±0.09[a]	0.34±0.15[a]	0.33±0.18[a]
LPS / ×10^{3}Eu·L^{-1}	0.14±0.03	0.16±0.04	0.21±0.02[a]	0.18±0.16	0.37±0.10[b]
Laclate / nmol·L^{-1}	9.03±2.19	18.30±2.56[a]	9.81±2.83	12.01±6.84	43.61±11.27[b]
L / M rat	0.03±0.01	0.41±0.27	0.62±0.20		1.70±0.60[b]
Intestinal pHi	7.03±0.05	7.05±0.06[b]	7.14±0.09[b]	7.20±0.08[a]	7.05±0.07[b]

[a]P<0.05; [b]P<0.01, *vs* before injury.

Table 3 Correlation analysis in goats subjected to hemorrhagic shock combined with endotoxin infusion

X	Y	r	P
DAO	TNFα	0.817	<0.01
DAO	LPS	0.842	<0.01
DAO	Laclate	0.872	<0.01
DAO	l / m	0.951	<0.01
DAO	Intestinal pHi	-0.553	<0.05

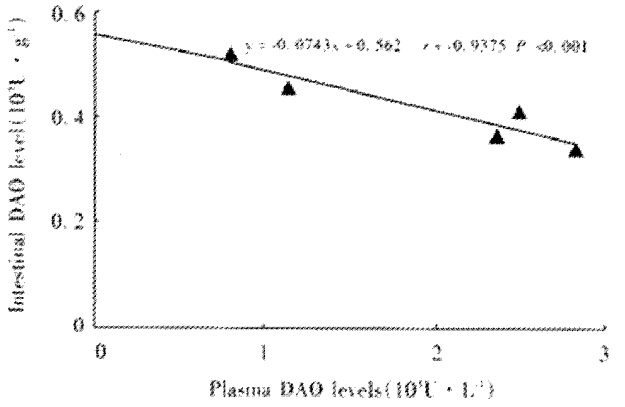

Figure 3 Relationship between intestinal and plasma DAO level.

DISCUSSION

DAO is located in the upper part of intestinal mucosa in human as well as in mammals, and is a highly active intracelluar enzyme. Under certain circumstances, intestinal mucosa cells became necrosed and dropped into the intestinal cavity, leading to decrease in intestinal mucosal DAO, and increase in DAO activity inside the intestinal cavity. DAO can also outer into the mucosal space between cells, lymphatic vessel[21-27] and blood flow, making plasma DAO markedly elevated. Gut as an important organ, may play an important role in the pathogenesis of serious complications. Intestinal mucosal surface layer with tight epithelial cells is an important component for intestinal barrier function, thus it can be seen that intestinal epithelial tissue integrated property is a key part to preserve intestinal barrier function. The changes in DAO activity is an ideal index to investigate intestinal barrier function damage after trauma, specially the changes in plasma DAO activity[2,6,10,11]. Therefore, intestinal barrier function injury after severe trauma could result in bacterial/toxin translocation, in turn evoke systemic inflammatory response syndrome

and multiple organ dysfunction syndrome[3,28-29].

The intestinal blood flow might keep relatively low despite of systemic circulation recovery during trauma, which was evident by significant decrease in intestinal mucosal pHi[30-33]. This may be the pathological basis for intestinal origin sepsis and multiple organ dysfunction syndrome. The changes in intestinal permeability were reflected by blood D-lactate and L/M rate in urine. Secretory IgA is an important component part for regulation intestinal immune function, it can prevent the bacteria from adhering to intestinal epithelial cells, and prevent gut-derived bacteria from invading through the intestinal barrier, which might reduce the toxicity of bacterial products to epithelial cells. Therefore, IgA may possess the beneficial effect on the preservation of intestinal mechanical barrier[34-37]. From our data that changes in several indexes of intestinal barrier function in various animal models after trauma, it was shown that DAO was released to increase in blood, and decreased in intestinal tissues. Thus, determination of DAO activity might reflect the condition of intestinal injury and repaired process.

The change in plasma D-lactate, lactulose, mannitol and ratio of L/M could reflect the increased intestinal permeability. The intestinal IgA levels appear to be associated with the local immunological dysfunction[38-41]. The change in intestinal pHi showed that intestinal hemorrhagic injury may result in the release of intestinal mucosal enzyme, subsequently leading to significant elevation of plasma DAO activity. This study showed that there is a close relationship between plasma DAO and TNFα, LPS, D-lactate, lactate, L/M, and the change of intestinal pathology and intestinal barrier function index was similar, indicating that intestinal barrier function was damaged after trauma.

We also observed that the plasma DAO activity was increased 2h and 72h after trauma, especially at 72h, and change of plasma TNFα and LPS was similar to the former. These results suggest that stress injury can cause changes of intestine barrier function index following intestinal ischemia-reperfusion injury, repair or endo/inextra protection, but the trends and degrees of changes were varied. Therefore, it is important to reduce development of SIRS to MODS by protection of intestinal barrier function in early trauma, and prevention of translation of intestinal origin bacteria and toxins[6,10,14,42-45].

Recent studies have shown that GLN may provide protection against intestinal barrier function injury after trauma[46-52]. Blood DAO activity was reduced to different extents at 10h,5d and 8d after early stage of oral GLN in scalded rats. Intestinal pathogical examination showed that the damage of epithetial cells of intestinal mucosa could be markedly improved, and the close correlation between plasma DAO and LPS and TNFα could also be changed after scalding[6]. The results indicate that GLN can protect against the intestinal barrier function damage after trauma.

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Edited by Ma JY