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BRIEF ARTICLE

Effects of intestinal mucosal blood flow and motility on intestinal mucosa

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Abstract

AIM: To investigate the role of intestinal mucosal blood flow (IMBF) and motility in the damage of intestinal mucosal barrier in rats with traumatic brain injury.

METHODS: Sixty-four healthy male Wistar rats were divided randomly into two groups: traumatic brain injury (TBI) group (n = 32), rats with traumatic brain injury; and control group (n = 32), rats with sham-operation. Each group was divided into four subgroups (n = 8) as 6, 12, 24 and 48 h after operation. Intestinal motility was measured by the propulsion ratio of a semi-solid colored marker (carbon-ink). IMBF was measured with the laser-Doppler technique. Endotoxin and D-xylose levels in plasma were measured to evaluate the change of intestinal mucosal barrier function following TBI.

RESULTS: The level of endotoxin was significantly higher in TBI group than in the control group at each time point (0.382 ± 0.014 EU/mL *vs* 0.102 ± 0.007 EU/mL, 0.466 ± 0.018 EU/mL *vs* 0.114 ± 0.021 EU/mL, 0.478 ± 0.029 EU/mL *vs* 0.112 ± 0.018 EU/mL and 0.412 ± 0.036 EU/mL *vs* 0.108 ± 0.011 EU/mL, $P < 0.05$). D-xylose concentrations in plasma in TBI group were significantly higher than in the control group (6.68 ± 2.37 mmol/L *vs* 3.66 ± 1.07 mmol/L, 8.51 ± 2.69 mmol /L *vs* 3.15 ± 0.95 mmol/L, 11.68 ± 3.24 mmol/L *vs* 3.78 ± 1.12 mmol/L and 10.23 ± 2.83 mmol/L *vs* 3.34 ± 1.23 mmol/ L, $P < 0.05$). The IMBF in TBI group was significantly lower than that in the control group (38.5 ± 2.8 PU *vs* 45.6 ± 4.6 PU, 25.2 ± 3.1 PU *vs* 48.2 ± 5.3 PU, 21.5 ± 2.7 PU *vs* 44.9 ± 2.8 PU, 29. 4 ± 3.8 PU *vs* 46.7 ± 3.2 PU) ($P < 0.05$). Significant decelerations of intestinal propulsion ratio in TBI groups were found compared with the control group (0.48% ± 0.06% *vs* 0.62% ± 0.03%, 0.37% ± 0.05% *vs* 0.64% ± 0.01%, 0.39% ± 0.07% *vs* 0.63% ± 0.05% and 0.46% ± 0.03% *vs* 0.65% ± 0.02%) ($P < 0.05$).

CONCLUSION: The intestinal mucosal permeability is increased obviously in TBI rats. Decrease of intestinal motility and IMBF occur early in TBI, both are important pathogenic factors for stress-related damage of the intestinal mucosal barrier in TBI.

Key words: Traumatic brain injury; Intestinal mucosa barrier; Stress; Intestinal mucosa blood flow; Intestinal motility

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INTRODUCTION

Multiple system organ dysfunction syndrome (MODS) often occurs following the stress of severe trauma, burn and acute necrotic pancreatitis[1-4]. However, its exact mecha-

nism remains unclear. The gut origin hypothesis suggests that damage of intestinal mucosal barriers as a result of these stress permits bacterial and endotoxin translocation, which triggers systemic immunoinflammatory response to release cytokines and inflammatory mediators. All of these might exacerbate systemic inflammatory response syndrome (SIRS) and MODS. Many patients with severe traumatic brain injury (TBI) often die of MODS[5], but not of the injury itself. So to prevent SIRS and MODS in TBI patients is one of the important factors that affect the prognosis and sequelea.

Our previous studies have found the damage of intestinal mucosal morphology and barrier function following TBI[6]. Although very common, the pathophysiology of this stress-related change is far from understood.

Fortunately, researches over the past decades have provided insight into the potential mechanisms responsible for the pathogenesis of stress-induced gastrointestinal dysfunction. The stressful situation is a multi-factorial disorder involving dysregulation within the brain-gut axis. Upon activation of the brain-gut axis by stress, the release of brain-gut peptides can profoundly affect gastrointestinal physiology and it is frequently associated with gastrointestinal motor, gastrointestinal mucosal blood flow (IMBF), enteric and central nervous system irregularities, and neuroimmune dysregulation[7].

The aim of this study was to further elucidate the effects of TBI on intestinal motility and IMBF, and to explore the putative mechanism of this stress-induced change in the TBI process.

MATERIALS AND METHODS

Animal model of TBI

Sixty-four healthy male Wistar rats, weighing 200-250 g (provided by Experimental Animal Center of Genetics and Developmental Biology Institute, Chinese Academy of Sciences), were randomly assigned to TBI model group (n = 32) and control group (n = 32). Each group was divided into four subgroups as 6, 12, 24 and 48 h after operation (n = 8). Experimental procedures complied with the ethical requirements for animal care.

Establishment of animal models

TBI group (n = 32): RATS with traumatic brain injury by free falling body method[8]. Rats were deprived of food for 12 h prior to experiment, and then was anesthetized with injection of 10% chloral hydrate (0.4 mL/100 g) and fixed on a stereotaxic apparatus. Scalp was cut along the median line and exposed the skull under steriled conditions. At the point of 2.0 mm rearward from the coronal suture and 2.0 mm left to the sagittal suture, open a 3.5 mm diameter bone window and maintain the integrity of the duramater. Then 20 g metal bar was released and fallen freely from 50 cm height to strike the meninges to cause the brain injury.

Control group (n = 32): rats with sham-operation with skull open operation alone and no brain injury.

Determination of endotoxin

One mL blood was collected from portal vein and placed into an apyrogenic tube (containing heparin) immediately. The levels of endotoxin were measured by chromogenic limulus amebocyte lysate test. The test kit was purchased from Shanghai Yihua Clinical Technology Company (Shanghai, China).

Measurement of D-xylose concentrations in plasma

Intestinal permeability was quantified by D-xylose concentrations in plasma. The 5% D-xylose solution of 1.5 mL was administered into the stomach by gastric tube feeding, and blood samples were collected into chilled tubes containing 100 U heparin 1 h later. The blood was centrifuged at 3000 r/min at 4℃ for 10 min. The plasma was stored at -70℃ until assayed. Levels of D-xylose in plasma were measured with D-xylose kit.

Measurement of IMBF

IMBF was measured with Laser Doppler Flowmetry (LDF) equipment (PeriFlux System 5000, Perimed, Sweden). The laser probe was inserted through a small enterotomy at the point that 20 cm from pylorus of the jejunal sac and held in a fixed position in the chamber solution at a distance of 1-2 mm above the mucosa. The measurement was taken as the average flow over a 10-min period following an initial 20-min period of stabilization.

Measurement of intestinal transit

Rats were fasted for 24 h prior to experiment, and 0.5 mL carbon-ink was administered into the stomach by gastric tube feeding. Twenty min later, the rats were killed at each time point, their intestines were removed from the pylorus through the ileocecal junction. The distance of carbon-ink from the pylorus to the most distal point of stain was expressed as migration distance. Results were expressed as propulsion ratio (%) of the migration distance to the total length of the small intestine (the distance between the pylorus and the ileocecal junction).

Statistical analysis

Software SPSS 11.0 was used for the statistical analysis. The data were expressed as mean ± SD. Experimental results were analyzed by unpaired t test and $P < 0.05$ was considered as significant difference.

RESULTS

Serum endotoxin levels

There were significant differences of endotoxin levels between the TBI group and control group at each time point (0.382 ± 0.014 EU/mL *vs* 0.102 ± 0.007 EU/mL, 0.466 ± 0.018 EU/mL *vs* 0.114 ± 0.021 EU/mL, 0.478 ± 0.029 EU/mL *vs* 0.112 ± 0.018 EU/mL and 0.412 ± 0.036 EU/mL *vs* 0.108 ± 0.011 EU/mL, $P < 0.05$, respectively). As shown in Table 1, the endotoxin was significantly increased 6 h after TBI, and reached the peak at 24 h, and then declined at 48 h, but was still higher than that of the control group.

Table 1 Changes of endotoxin in plasma (mean ± SD) (EU/mL)

Groups	6 h	12 h	24 h	48 h
Control	0.102 ± 0.007	0.114 ± 0.021	0.112 ± 0.018	0.108 ± 0.011
TBI	0.382 ± 0.014[a]	0.466 ± 0.018[a]	0.478 ± 0.029[a]	0.412 ± 0.036[a]

[a]$P < 0.05$ *vs* control. TBI: Traumatic brain injury.

Table 2 Changes of D-xylose in plasma (mean ± SD) (mmol/L)

Groups	6 h	12 h	24 h	48 h
Control	3.66 ± 1.07	3.15 ± 0.95	3.78 ± 1.12	3.34 ± 1.23
TBI	6.68 ± 2.37[a]	8.51 ± 2.69[a]	11.68 ± 3.24[a]	10.23 ± 2.83[a]

[a]$P < 0.05$ *vs* control. TBI: Traumatic brain injury.

Table 3 Changes of intestinal mucosal blood flow (mean ± SD) (PU)

Groups	6 h	12 h	24 h	48 h
Control	45.6 ± 4.6	48.2 ± 5.3	44.9 ± 2.8	46.7 ± 3.2
TBI	38.5 ± 2.8	25.2 ± 3.1[a]	21.5 ± 2.7[a]	29.4 ± 3.8[a]

[a]$P < 0.05$ *vs* control. TBI: Traumatic brain injury.

Table 4 Ratio of intestinal propulsion (mean ± SD) (%)

Groups	6 h	12 h	24 h	48 h
Control	0.62 ± 0.03	0.64 ± 0.01	0.63 ± 0.05	0.65 ± 0.02
TBI	0.48 ± 0.06[a]	0.37 ± 0.05[a]	0.39 ± 0.07[a]	0.46 ± 0.03[a]

[a]$P < 0.05$ *vs* control. TBI: Traumatic brain injury.

D-xylose concentrations in plasma

D-xylose concentrations in plasma in TBI rats were significantly higher than in the control group (6.68 ± 2.37 mmol/L *vs* 3.66 ± 1.07 mmol/L, 8.51 ± 2.69 mmol/L *vs* 3.15 ± 0.95 mmol/L, 11.68 ± 3.24 mmol/L *vs* 3.78 ± 1.12 mmol/L and 10.23 ± 2.83 mmol/L *vs* 3.34 ± 1.23 mmol/L, $P < 0.01$, respectively), indicating that the intestinal mucosal barrier was damaged (Table 2).

Changes of IMBF

As shown in Table 3, IMBF was significantly lower in TBI group than that in the control group (38.5 ± 2.8 PU *vs* 45.6 ± 4.6 PU, 25.2 ± 3.1 PU *vs* 48.2 ± 5.3 PU, 21.5 ± 2.7 PU *vs* 44.9 ± 2.8 PU, 29. 4 ± 3.8 PU *vs* 46.7 ± 3.2 PU) ($P < 0.05$). It began to decrease at 6 h, reached the lowest at 24 h, and did not reach the baseline by 48 h.

Changes of intestinal transit

The overall mean ratio of intestinal propulsion under TBI stress was lower than that of the control group (0.48% ± 0.06% *vs* 0.62% ± 0.03%, 0.37% ± 0.05% *vs* 0.64% ± 0.01%, 0.39% ± 0.07% *vs* 0.63% ± 0.05% and 0.46% ± 0.03% *vs* 0.65% ± 0.02%) ($P < 0.05$), indicating that TBI stress could inhibit small intestinal motility (Table 4).

DISCUSSION

Gastrointestinal dysfunction is a common complication of stress. Damage of the gastrointestinal function, especially of the gastrointestinal barrier function, permits translocation of enterogenic bacteria and endotoxins, triggers systemic immunoinflammatory response to release cytokines and inflammatory mediators, which is an important initiator as well as a stimulator for occurrence of SIRS, sepsis and MODS following major stress[9]. The stress including severe trauma, hemorrhagic shock, severe pancreatitis and burn[10,11]. So the gastrointestinal barrier function is one of the important factors that affect the prognosis and sequelea.

Intestinal mucosal barrier function could be evaluated by measuring the permeability of saccharide molecular probe. Lactulose/mannitol and D-xylose have previously been used to assess intestinal mucosal permeability[12-15]. Shi *et al*[16], reported that chronic restraint stress could cause damage of the intestinal barrier function and increased intestinal permeability to D-xylose.

In this study, we used endotoxin and plasma D-xylose to evaluate the intestinal mucosa barrier function. We found that the endotoxin and plasma D-xylose levels in the TBI group were significantly higher than in the control group at 6 h following TBI, and reached its peak at 24 h, and then declined at 48 h, but still markedly higher than that in the control group. All of these demonstrated that TBI stress could be an initiating factor to increase the permeability of intestinal mucosa, suggesting that the intestinal mucosal barrier dysfunction initiated at the early stage of TBI.

At present, the specific pathogenesis and progress of the intestinal mucosal barrier damage still remain unclear. Stress is known to alter ingestive behaviors and associated physiological events such as gastric acid secretion and gastrointestinal motility. Mast cells translate the stress signal that has been transmitted through brain-gut axis to release a wide range of neurotransmitters and proinflammatory mediators, some of them are brain-gut peptides, such as 5-HT, SP, CGRP, CRP, CCK, NO, NE and VIP. Evidences implicated that the brain-gut peptides are involved in these physiological effects which can change the intestinal motility, modulate tight junction proteins and increase the intestinal permeability[7,17]. Animal studies suggest that cholecystokinin (CCK) acts *via* a vagal afferent pathway to decrease gastrointestinal motility[18] and substance P can stimulate a contractile function of smooth muscle[19]. Studies in animal models showed that burn injury and cardiopulmonary bypass markedly down-regulated the expression of occludin and tight junction associated protein ZO-1 in intestinal mucosa of rats. The close correlation between expression of tight junctions and plasma levels of diamine oxidase or *d*-lactate supports the hypothesis that intestinal permeability increases during and after stress events because of decreases in the expression of tight junctions[20,21].

IMBF plays a vital role in intestinal mucosal defense system. Sufficient IMBF brings oxygen and nutrients to the mucosal cells, maintains the normal structure and function of intestinal mucosa and is closely associated with the pathogenesis and healing of intestinal mucosal lesions[22]. Our results revealed that IMBF decreased significantly at the early stage of TBI, and the intestinal mucosal permeability increase occurred at the same time. As intestinal mucosa is very sensitive to the shortage of blood and oxygen, ischemia/reperfusion (I/R) is the main pathogenesis of intestinal mucosal damage. The physiopathology of intestinal mucosal damage by I/R is not fully understood. But, it is believed that cytotoxic substances such as free radicals, nitric oxide, pro-inflammatory cytokines, leukotrienes, serotonin and other related products, play important roles[23,24]. I/R not only damages the intestinal mucosal barrier function but also alters the gastrointestinal motility[25].

It is widely believed that delayed intestinal motility could cause small intestinal bacterial overgrowth (SIBO). Gangarosa[26] demonstrated that intestinal motility served as a normal cleansing mechanism of the intestine. Leveau *et al*[27] noticed a delay in intestinal transit time, appearing as an early event in acute pancreatitis, preceding SIBO, and suggested that impairment in intestinal motility may play a role in the development of SIBO. Tsukada *et al*[28-30] demonstrated that the small intestinal transit was significantly inhibited by restraint stress. Our results revealed that, at the early stage of TBI, the intestinal propulsion ratio decreased significantly as compared with control group ($P < 0.05$). Damage of intestinal mucosal barrier function occurred at the same time, indicating that the inhibition of intestinal motility might be another vital factor of gastrointestinal barrier dysfunction.

The mechanism may be explained by the fact that the prolonged small intestinal transit makes it possible that the small intestinal content remains in the intestinal tract for a long time, preceding SIBO, increasing the chance of bacterial and endotoxin translocation and producing a great deal of gas. The defect of intestinal barrier and the above factors of small intestinal dysfunction may enhance each other.

In summary, the damage of intestinal mucosal barrier function following TBI is caused by multiple factors, the close correlation between decrease of intestinal blood flow and motility and increase of intestinal permeability supports the hypothesis that both of them might play a very important role in the regulation of intestinal epithelial barrier dysfunction during and after TBI. Therefore, maintaining intestinal barrier function is a systematic engineering project. Further research that more precisely characterizes the role of intestinal mucosal blood flow and intestinal motility in these diseases could put new insights into the new therapies for stress-induced injury of intestinal mucosal barrier function.

COMMENTS

Background

Multiple system organ dysfunction syndrome (MODS) often occurs following the stress of traumatic brain injury (TBI). Athough being very common, the pathophysiology of this stress-related change is far from understood. The gut origin hypothesis suggests that damage of intestinal mucosa barriers as a result of these stress permits bacterial and endotoxin translocation, which triggers systemic immunoinflammatory response to release cytokines and inflammatory mediators. All of these might exacerbate the systemic inflammatory response syndrome (SIRS) and MODS.

Research frontiers

Gastrointestinal dysfunction is a common complication of stress. Damage of gastrointestinal function, especially of the gastrointestinal barrier function is an important initiator as well as a stimulator for occurrence of SIRS, sepsis and MODS following major stress, including severe trauma, hemorrhagic shock, severe pancreatitis and burn. Studies in animal models showed that brain-gut axis/ brain-gut peptides are involved in these physiological effects which can change the intestinal motility, modulate tight junction proteins and increase intestinal permeability.

Innovations and breakthroughs

The specific pathogenesis and progress of stress-induced damage of intestinal barrier function remain unclear. But, disruption of the intestinal mucosal protection is certainly involved. Intestinal blood flow plays a vital role in intestinal mucosal defense system and intestinal motility served as a normal cleansing mechanism of the intestine. This study revealed that the intestinal blood flow and motility decreased significantly at the early stage of TBI, and the intestinal mucosal permeability increase occurred at the same time. The results suggested that both might be important pathogenic factors for intestinal barrier function damage during and after TBI.

Applications

Many patients with severe TBI often die of MODS, but not of the injury itself. So to protect the mucosal barrier function at the early stage of TBI will be of significance for reducing the stress-related SIRS and MODS.

Terminology

Brain-gut axis is composed of main regulatory cores in the central nervous system that are connected to peripheral (enteric and autonomic) nervous systems through a series of networks of afferent and efferent nerves. Brain-gut peptide is named because of its distribution in both nervous system and gastrointestinal tract. Intestinal mucosal barrier function include mechanical barrier, chemical barrier, immunologic barrier and biological barrier, any damage of these barriers will damage the intestinal mucosal barrier function.

Peer review

This is a well conducted randomized controlled trial on animal models. The authors presented the results of their study that decreased intestinal blood flow and motility occur early in TBI, which supports the hypothesis that both are important pathogenic factors for increasing the intestinal permeability. So resuming the intestinal blood flow and motility might be a useful method for maintaining intestinal barrier function during and after TBI.

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