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• BRIEF REPORTS •

Effects of intestinal lymph on expression of neutrophil adhesion factors and lung injury after trauma-induced shock

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Abstract

AIM: To study how intestinal lymph after trauma-induced shock (TIS) interferes with expression of neutrophil adhesion factors (CD11b and CD18) and causes lung injury.

METHODS: Thirty-two adult healthy Sprague-Dawley rats were randomly divided into four experimental groups. Groups 1 and 2 included rats with TIS caused by hitting the mid-upper part of both side femoral bones with a 2 500 kg raw-iron, and with or without ligation of mesenteric lymph duct. Groups 3 and 4 included rats with sham-TIS and with or without ligation of mesenteric lymph duct. Expression of neutrophil CD18 and CD11b in at 1 and 3 h after a 90-min TIS/sham-TIS was evaluated. These rats were killed at 3 h after TIS/sham-TIS, and lungs were taken immediately. The main lung injury indexes (the MPO activity and lung injury score) were measured.

RESULTS: The expressions of CD18 and CD11b at 1 and 3 h after a 90-min TIS and the main lung injury indexes were significantly increased compared with those in the sham-TIS groups ($P<0.05$). Moreover, at 1 and 3 h after TIS, the expressions of CD18 (32.12±1.25 and 33.46±0.98) and CD11b (29.56±1.35 and 30.56±1.85) were significantly decreased in rats with ligation of mesenteric lymph duct, compared with those (52.3±1.12 and 50.21±1.25, and 42.24±1.24 and 42.81±1.12, respectively) in those without the ligation (all $P<0.05$). The main lung injury indexes in rats with TIS with ligation of mesenteric lymph duct (0.96±0.12 and 6.54±0.35) were also significantly decreased, compared with those (1.56±0.21 and 9.56±0.23) in rats with TIS without the ligation (both $P<0.05$). However, there was no significant difference in expressions of CD18 and CD11b and the main lung injury indexes between the two sham-TIS groups.

CONCLUSION: Previous ligation of mesenteric lymph ducts prevents or alleviates the up-regulated expression of PMN CD18 and CD11b and the lung injury induced by TIS. Our findings also indicate that neutrophil adhesion molecule activation and lung injury during TIS appear to be caused by some factors that are released or produced by post-ischemic intestine through the mesenteric lymph pathway.

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INTRODUCTION

Trauma-induced-shock (TIS) could lead to splanchnic ischemia-reperfusion and gut barrier failure[1]. These events could get the gut into an inflammatory cytokine-secreting organ, which contributes to the pathogenesis of shock-induced lung injury[2,3]. Lung injury generally occurs when mediators released by systemic inflammatory processes up-regulate polymorphonuclear neutrophil (PMN) interactions with endothelial cells (ECs), thus favoring PMN sequestration and attack on the lung. Shock and trauma-induced neutrophil activation has been implicated in the pathogenesis of adult respiratory distress syndrome (ARDS) and also as a contributory factor in the development of multiple organ dysfunction syndrome (MODS)[4,5]. Furthermore, enhanced endothelial-neutrophil interactions resulting in tissue injury appear to be the common pathways by which diverse initiating factors, such as bacterial infection, endotoxin, cytokines, shock, and ischemia can lead to organ injury and MODS[6]. These events have been implicated in the pathogenesis of pulmonary microvascular injury after intestinal ischemia-reperfusion injuries[7,8].

However, the exact mechanisms by which intestinal ischemia reperfusions subsequent to trauma and hemorrhage primes neutrophils remain uncertain. There are many discussions about this topic. Since Gonzalez *et al*. demonstrated that port vein blood did not contain such inflammatory mediators in patients with traumatic shock, such as endotoxin or bacteria, more and more people have attached importance to lymph pathway[9]. Some study in a rat model of trauma-hemorrhagic shock (T/HS) has shown that ligation of the main mesenteric lymph draining the intestine could prevent lung injury[10], and furthermore, it has been testified that mesenteric lymph from rats subjected to T/HS can prime neutrophils for an oxidative burst[11]. TIS mesenteric lymph can activate PMNs and increase their ability to injure ECs, and on the other hand, PMN exposure to mesenteric lymph is both necessary and sufficient for the activation of rat PMN respiratory burst by TIS. From a mechanical point of view, respiratory burst activation in response to G-protein-coupled agonists is characterized by enhanced cell calcium [Ca2+]i) flux response to GPC agonists tested[12,13]. In contrast, portal plasma from TIS rats lacks the potential to activate PMNs.

All these studies lead to the conclusion that lymph from the ischemic gut may be a crucial source of neutrophil priming factors after major hemorrhagic insults, such as lung injury, systemic inflammatory response syndrome (SIRS), MODS, and multiple system organ failure (MSOF). Therefore it has come to be accepted by more and more people that gut-induced lung injury is secondary to a shock-induced gut "inflammatory state", where gut-induced inflammatory factors enter the systemic circulation via mesenteric lymphatics rather than via portal bloodstream. To testify and further extend this concept that neutrophil priming activation was caused by release of factors

from gut into the mesenteric lymphatics, we performed this experiment to study whether TIS could up-regulate neutrophil adhesion molecule expression and cause lung injury, and whether such pathological changes could be prevented or alleviated by ligating mesenteric lymph ducts previously.

MATERIALS AND METHODS

Animals

Adult Sprague-Dawley rats (SD rats) weighing 300-350 g were used after a minimum acclimatization period of 7 d. The animals and their diet were provided by The Laboratory Animal Center, Zhejiang University, College of Medicine, China. The animals were had free access to food and water and were maintained in accordance with the guideline of the National Guide for the Care and Use of Laboratory Animals, and the experiment was approved by the Zhejiang University, College of Medicine.

Experimental design

The aim of this experiment was to assess how the lymph after TIS affected the expression of neutrophil adhesion molecules and caused lung injury in rats. Four groups were included. They were groups of rats subjected to TIS with or without mesenteric lymph duct ligation, and groups of rats subjected to sham TIS with or without mesenteric lymph duct ligation. Femoral artery blood samples were collected 1 and 3 h after a 90-min shock period for further evaluating the expression of PMN. Then these rats were killed immediately, lungs were removed for assessment of the severity of injuries, mainly by measuring myeloperoxidase (MPO) content and lung injury score.

TIS model

As previously described[14], rats were anesthetized intraperitoneally using sodium pentobarbital (50 mg/kg), and a femoral artery catheter was placed for measuring the artery pressure and an other side femoral artery catheter for taking blood. Then a midline laparotomy was performed to expose the mesenteric lymph duct, which was either ligated with 2-0 silk or just left intact according to the experimental need. The incision was closed. A 2 500 kg raw- iron was used to hit the rat's mid-upper part of both side femoral bones from 30 cm height to cause TIS, then the rat artery pressure was maintained at about 30 mmHg for 90 min, by blood withdrawal or normal saline infusion through one side of the femoral artery catheter, the other side of femoral artery catheter was used to measure the artery pressure. The rats were subjected to TIS for 90 min and then their traumatic legs were tied up closely. The animal body temperature during the experiment was maintained at about 37 ℃ by using a heating pad.

Sham-TIS model

Except trauma treatment and being subjected to shock state, the sham-TIS model accepted the nearly same treatment as TIS model.

Assay of blood CD11 b and CD18

Blood sample (1 mL) collected at 1 and 3 h after 90 min of TIS/sham-TIS state was collected and treated with anti-coagulant EDTANa2. A 100 μL blood sample was put into a 12 mm×75 mm tube and then 10 μL anti-rat CD11b or CD18 fluorescent labeled monoclonal antibody (BD Pharmingen) was added into the tube. The samples were gently vortexed for 10 min and then placed into a dark room for 40 min. Red blood cells of the sample were lysed and fixed with Coahem Q-PREP equipment (Couletr Company, USA) for 15 min on ice. After centrifuged and washed 3 times, PMN cells were analyzed for adhesion molecule expression using flow cytometer (ESPLL-XL, BECKMAN, USA) according to the recommendation of the manufacturer. The number of these neutrophils labelled with monoclonal antibody in 10 000 neutrophils was counted and the percentage was evaluated.

Assay of myeloperoxidase

Three hours later, rats were killed and the right lung was immediately taken and frozen. The frozen lung tissue was homogenized and processed for measuring myoloperoxidase (MPO) with the regent kit (Jiancheng Bio-Technology Company, Nanjing, China) according to the manufacturer's instructuons. One unit of MPO activity represented the amount of enzyme that reduced 1 μmol/L of peroxidase per minute.

Assay of lung injury sore

The lung tissue was fixed in 40 g/L formaldehyde, cut into 4 μm sections and stained with HE. The lung injury score (LIS)[15] was evaluated with OLMPUS optical microscope (Olympus, Japan). The severity of leukocyte sequestration in the lung tissue was classified as: 0 = 0%, 1 = 0-25%, 2 = 25-50%, 3 = 50-75%, 4 = 75-100%. The severity of leukocyte sequestration in lung alveoli was classified as: 0 = none, 1 = few, 2 = a lot, 3 = almost all, 4 = all. The severity of exudation (such as fibrin, transparent membrane and edema liquor) in lung alveoli was classified as: 0 = none, 1 = few, 2 = a lot, 3 = almost full, and 4 = absolute full.

Statistical analysis

Results were expressed as mean±SD. The data were analyzed with SPSS.11.0. The comparison among multiple groups was made with *t* test. Probabilities less than 0.05 were considered statistically significant.

RESULTS

The expressions of CD18 and CD11b in PMN were significantly increased after TIS with or without ligation of mesenteric lymph ducts compared with sham shock groups ($P<0.05$, Table 1). Both CD18 and CD11b expressions were up-regulated by the TIS pathological process. The expressions of CD18 and CD11b in sham shock with or without ligation of mesenteric lymph duct had no significant difference ($P>0.05$). It showed that ligation of mesenteric lymph duct itself had no effect on the expression of CD18 or CD11b. The results also showed that the expressions of CD18 and CD11b after TIS with ligation of mesenteric lymph duct were significantly decreased as compared with TIS without ligation of lymph duct ($P<0.05$). It was suggested that previous ligation of mesenteric lymph duct during TIS could down-regulate the expressions of CD18 and CD11b.

Table 1 Comparison of expressions of CD18 and CD11b in ratsof all groups at 1 and 3 h after 90 min of TIS/sham-TIS state(%)

Group	CD18		CD11b	
	1st h	3rd h	1st h	3rd h
TIS with ligation of mesenteric lymph duct (8)	32.12±1.25	33.46±0.98	29.56±1.35	30.56±1.85
TIS without ligation of mesenteric lymph duct (8)	52.3±1.12	50.21±1.25	42.24±1.24	42.81±1.12
Sham TIS with ligation of mesenteric lymph duct (8)	17.02±0.95	15.68±0.98	14.02±1.23	13.63±1.23
Sham TIS withtout ligation of mesenteric lymph duct (8)	16.23±1.20	16.25±0.53	13.61±1.25	13.51±1.65

The main lung injury indexes (MPO activity and lung injury score) of TIS group were significantly increased compared with sham shock group ($P<0.05$, Table 2). The results showed that the main lung injury indexes of sham shock groups with or without ligation of mesenteric lymph duct had no significant difference ($P>0.05$). It seemed that ligation of mesenteric lymph duct itself could not cause lung injury. The results also showed that the MPO activity and lung injury score of TIS with previous ligation of mesenteric lymph duct were significantly decreased as compared with TIS without ligation of lymph duct ($P<0.05$). It appeared that previous ligation of mesenteric lymph duct could alleviate lung injury effectively during TIS.

Table 2 Comparison of MPO activity and lung injury score in rats of all groups

Group (n = 8)	MPO activity (Ug^{-1} lung tissue)	LTS
TIS witht ligation of mesenteric lymph duct	0.96±0.12	6.54±0.35
TIS without ligation of mesenteric lymph duct	1.56±0.21	9.56±0.23
Sham TIS witht ligation of Mesenteric lymph duct	0.45±0.05	2.35±0.56
Sham TIS withtout ligation of Mesenteric lymph duct	0.50±0.08	2.53±0.41

DISCUSSION

It has been found that the phenomena of neutrophil activation is often companied by TIS, and that activated neutrophils may play a key role in the pathogenesis of lung injury or MODS, MSOF in TIS[16]. But the mechanism of neutrophil activation, lung injury or MODS is still uncertain. Therefore, the soluble factors in neutrophil activation subjected to TIS and the cellular mechanisms for neutrophil activation are the hot topics. A lot of evidence showed that ischemia-reperfusion gut was an important source of factors that might cause neutrophil activation, lung injury or MODS after TIS[17-19]. Post-ischemia gut has been shown to be a cytokine-generating organ, and the vascular bed of post-ischemia has been proven to be a priming bed for neutrophils by both clinical and experimental studies[20]. It is usually believed that the loss of gut barrier function in shock states leads to bacterial translocation. Then such a bacterial translocation might cause sepsis and organ dysfunction in TIS patients. However, studies about TIS showed that neither bacteria nor endotoxin was found in portal blood of severely injured trauma patients. These findings have made people to doubt the theory of bacterial translocation during TIS.

It has been shown that the TIS induced increase in pulmonary capillary permeability could be prevented by ligation of mesenteric lymph ducts[21], and mesenteric lymph from rats subjected to TIS, but not sham TIS could injure endothelial cells and increase their permeability[22]. Shock-induced up-regulation of pulmonary endothelial P-selection expression could also be alleviated by mesenteric lymph duct ligation.

Based on these clinical and experimental findings, people come to hypothesize that lymphatics might be the primary route by which intestinal factors leave the gut and cause subsequent injury of lung or other organs instead of portal route. Neutrophil-endothialial interaction is involved in endothelial cell injury and endothelial cell adhesion molecule up-regulation. In order to investigate this hypothesis, we designed these experiments. To explore how TIS lymph affected PMN activation and lung injury, we compared TIS rats with or without ligation of the mesenteric lymph ducts. CD18 and CD11b were chosen as the indicators of PMN activation, and MPO and lung injury score were chosen as the indicators of lung injury[23,24].

The results of our study showed that the expressions of PMN CD18 and CD11b and the main lung injury indexes (the MPO activity and lung injury score) of TIS at 1 and 3 h after 90 min of TIS state were significantly increased compared with those of sham shock group, but had no significant difference between two sham shock groups with or without ligation of mesenteric lymph ducts. The results also showed that previous ligation of mesenteric lymph ducts could down-regulate the expressions of CD18 and CD11b and alleviate lung injury in rats subjected to TIS. These results are consistent with the studies of Harkin *et al*.[25], who showed that mesenteric ligation prevented shock-induced CD11b up-regulation using a less severe shock model. The theory that the gut is a primary source of neutrophil-activating factors is consistent with our study and Adams *et al*.[26], who found that the ability of plasma from rats subjected to TIS to prime neutrophils for an augment respiratory burst was lost after lymph duct ligation.

Generally, it seems that factors contained in TIS intestinal lymph are both necessary and sufficient to account for neutrophil activation and priming after TIS. The intestine could produce a wide rage of inflammatory mediators, including cytokines, eicosanods, oxidants, platelet-activating factors, complement fragments, and endotoxin[27,28]. Many of these mediators can prime or activate neutrophils and endothelial cells directly or indirectly. It has been proven that primed and activated neutrophils are involved in the pathogenesis of posttraumatic inflammatory syndromes such as systemic inflammatory response syndrome (SIRS), adult respiratory distress syndrome (ARDS), MODS, and MSOF. It also has been testified that prevention of tissue neutrophil infiltration can reduce lung and other organ injury in the models of TIS[29]. The results of our experiment also showed that pathologic neutrophil activation by gut lymph was critical to the pathogenesis of TIS.

Since no bacteria or endotoxin was found in mesenteric lymph subjected to TIS, further work is needed to study on the characterization and identification the nertophil-activating factors in the TIS lymph. It has ever been thought that the lipid fraction of lymph was responsible for neutropil activation[30]. However, Daysl *et al*.[31] pointed out that the respiratory burst of rat neutrophils was stimulated by the aqueous but not lipid fraction of the lymph samples. The exact explanation for these conflicting results is not known, but it may suggest that TIS lymph contains several factors which are capable of activating neutrophils. So, further study may still be needed to define the factors in TIS gut lymph which could activate neutrophils and cause injury of lung or other important organs.

In conclusion, mesenteric lymph after TIS contains multiple biologically active agents. These agents have the potential to modify both PMN and EC behaviors, which are probably involved in the pathogenesis of lung injury after TIS. The results showed that up-regulated expressions of PMN CD18 and CD11b and the lung injury induced by TIS could be prevented or alleviated by previous ligation of mesenteric lymph ducts. These findings may indicate that lung injury during TIS is caused by PMN adhesion molecule activation induced by some factors released or produced by postischemic intestine through mesenteric lymph pathway rather than traditionally believed portal vein.

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