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BETA-GLUCAN ATTENUATES INFLAMMATORY CYTOKINE RELEASE AND PREVENTS ACUTE LUNG INJURY IN AN EXPERIMENTAL MODEL OF SEPSIS

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ABSTRACT—Sepsis is one of the most important risk factors in acute respiratory distress syndrome (ARDS). β-Glucan is a potent reticuloendothelial modulating agent, the immunobiological activity of which is mediated in part by an increase in the number and function of macrophages. In this study, we investigated the putative protective role of β-glucan against sepsis-induced lung injury. Sepsis was induced by cecal ligation and puncture (CLP) in Wistar rats. The control group received saline, and the treatment groups received β-glucan or β-glucan + β-1,3-D-glucanase. Five hours thereafter, plasma tumor necrosis factor (TNF) α, interleukin (IL) 1β, and IL-6 levels were determined. Presence of lung injury was determined via lung tissue myeloperoxidase (MPO) activity, intercellular adhesion molecule (ICAM) 1 levels, and histopathological examination at 18 h after CLP. In a separate set of experiments, survival was monitored for 7 days after CLP. β-Glucan treatment led to a significant increase in survival rate (63% in glucan-treated rats vs 38% in saline-treated rats). Administration of the β-glucan inhibitor abrogated β-glucan's survival benefit (50%). After CLP, plasma TNF-α, IL-1β, and IL-6 concentrations were increased in control animals. When β-glucan was administered, it completely blocked the elevation of TNF-α, IL-1β, and IL-6. Administration of β-1,3-D-glucanase suppressed glucan-induced decrease in cytokines. Animals treated with β-glucan showed a significant reduction in lung injury score, a marked decrease in ICAM-1 expression, and a significant decrease in MPO levels. In contrast, β-1,3-D-glucanase caused a significantly increased MPO and ICAM-1 levels in the lung. These data reveal that β-glucan treatment improved the course of CLP-induced peritonitis and attenuated the lung injury. Administration of β-glucanase inhibited the β-glucan activity and resulted in enhanced lung injury.

KEYWORDS—Inflammation, β-glucan, cecal ligation and puncture, acute lung injury, ICAM-1

INTRODUCTION

Sepsis is the most common predisposing condition leading to the acute respiratory distress syndrome (ARDS) and is associated with the highest mortality among causes of this condition (1). Acute respiratory distress syndrome has been characterized as a disease state, in which the inflammatory balance is shifted toward tissue injury. Excessive inflammatory reactions and, in particular, neutrophil activation have been implicated in pathogenesis of ARDS (2, 3). Instead, the initiation of a systemic inflammatory response in the host appears to be a critical step in the pathogenesis of ARDS (4). The development of sepsis is associated with activation of complex cytokine cascades. The systemic production of early-response proinflammatory cytokines, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 results in a number of inflammatory events, including widespread inflammatory cell recruitment and activation (5). During the complex array of cell-cell interactions in the development of inflammatory processes, expression of vascular adhesion molecules such as intercellular adhesion molecule (ICAM) 1 plays a fundamental role leading to adhesion of leukocytes to the activated endothelium and subsequent transmigration of leukocytes into the extravascular areas (6).

To develop therapeutic strategies for sepsis, it is necessary to clarify the precise mechanisms that link an infection in a primary tissue compartment with systemic manifestations of inflammation and distant organ injury. Inflammatory mediator-targeted therapies were promising early on; however, larger trials have found therapies such as cytokine modulation, platelet-activating factor inhibition, and neutrophil elastase inhibitors to be ineffective in the treatment of ARDS (7). One of the recent alternatives to classical antibiotic treatment is the use of immunomodulators for enhancing host defense responses. Several types of immunomodulators have been identified, including mammalian proteins such as interferon γ, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, as well as substances isolated and purified from microorganisms (8). The latter type of immunomodulators typically induces nonspecific stimulation of the immune system (9, 10).

We recently identified that β-glucan, an immunomodulator polysaccharide, decreased weight loss, anastomotic leakage, and mortality in septic rats (11). However, the possibility that β-glucan could have prevented lung injury had not been determined, as we have done in the present study. We evaluated the effect of β-glucan on acute lung injury after experimental peritonitis by using a rat cecal ligation/puncture (CLP) model. Cecal ligation/puncture in rodents has been extensively used as a suitable experimental model to study the etiopathology of septic shock and to develop more effective

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pharmacological agents to control this complex condition (12). In addition, we tested the effect of β-glucan on expression of the ICAM-1 on alveolar epithelial cells and assessed their functional implications.

MATERIALS AND METHODS

Animal preparation

The experimental protocols were conducted with the approval of the Animal Research Committee at Gazi University, Ankara, Turkey. All animals were maintained in accordance with the recommendations of the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

Animals and experimental design

Male Wistar rats weighing 230 to 280 g were housed individually in cages and were allowed free access to standard rat chow with free access to tap water. The animal rooms were windowless with temperature (22°C ± 2°C) and lighting controls. The animals were made to fast overnight before the experiments but were given free access to water. They were anesthetized by ketamine 100 mg/kg and xylazine 20 mg/kg body weight i.p. They breathed spontaneously throughout the procedures. The abdominal skin was disinfected with 70% alcohol. All procedures were performed under sterile conditions. A midline incision was made approximately 3-cm long, sufficient to expose the cecum and adjoining intestine. Polymicrobial peritonitis was produced by CLP as follows. The cecum was exposed, ligated with a 3/0 silk suture just distal to the ileocecal valve to avoid intestinal obstruction, punctured twice with a 22-gauge needle. The cecum was gently squeezed to extrude feces and to endure that the 2 puncture holes did not close and then returned to the abdominal cavity. The abdominal incision was closed with 3/0 silk sutures in layers. Saline (3 mL/100 g of body weight) was administered subcutaneously to each rat after CLP. After the operation, animals were kept in individual cages, and they were deprived of food but had free access to water. The rats were divided into 4 groups (n = 18 per group) in randomized manner; sham, control, β-glucan, and β-glucan + β-glucanase. In sham-operated controls, animals were anesthetized, subjected to laparotomy and cecal manipulation, and closed. Control group received isovolumetric saline solution, β-glucan group received 2 mg/kg (0.6 mg/mL water, 30 min, 55°C) β-D-glucan (Sigma Chemical Company, St Louis, Mo), and β-glucan + β-glucanase group received 2 mg/kg β-D-glucan and 1 mg/kg (5 mg/mL 0.1 mol/L phosphate, pH 7.0) β-1,3-D-glucanase (Sigma Chemical Company) i.m. just after CLP with an additional one injection at 4 h after CLP.

Ten anesthetized rats from each group were killed by exsanguination at 18 h after CLP or sham operation. Lungs were also harvested for tissue studies. Necropsy was performed on all animals to control absence of surgically related complications.

Survival studies

Eight animals in each group were used for the analysis of survival. The survival rate was calculated from the number of animals living longer than 7 days after operation.

Cytokine detection

Blood samples were obtained and placed in microcentrifuge tubes 5 h after CLP or sham operation, and plasma was separated by centrifugation, immediately frozen, and stored at −80°C until the time of assay. Plasma TNF-α, IL-1β, and IL-6 levels were detected in a 96-well microtiter plate by the use of a commercial enzyme-linked immunosorbent assay (ELISA) kit (BioSource International, Inc, Camarillo, Calif) according to the manufacturer's guidelines. All samples were tested in the duplicate. The plate was read on EL×800 automated microplate reader (Bio-Tek Instruments, Inc, Winooski, Vt) at 450 nm. The concentrations of TNF-α, IL-1β, and IL-6 were calculated from a standard curve and expressed in picograms per milliliter. The lower limit of detection for ELISA was 8 to 16 pg/mL.

Lung myeloperoxidase activity assay

At 18 h after CLP or sham operation, lungs isolated from the animals were rinsed with saline and blotted dry. After weighing, lung tissue was homogenized in a 1.2-mL 20 mmol/L potassium phosphate buffer, pH 7.4, and centrifuged for 30 min at 30,000g, at 4°C. The pellet was resuspended in phosphate-buffered saline, pH 6.0, containing 0.5% hexadecyltrimethylammonium bromide. The resuspended pellets were frozen at −70°C until the MPO activity assay was performed. The supernatant, 0.1 mL, was added to 2.9 mL of 50 mmol/L potassium phosphate buffer, pH 6.0, containing 0.167 mg/mL o-dianisidine, and 0.0005% hydrogen peroxide, and the absorbance of 460-nm visible light was measured for 3 min. The MPO activity per gram wet lung was calculated as follows: MPO activity (U/g lung) = $\Delta A \times 4.05$/lung weight (g). ΔA is equal to rate of change in absorbance at 460 nm between 1 and 3 min.

Histology

Histological studies were performed on lungs harvested from the animals after killing in each group. Specimens were prepared as previously described, processed, and stained with hematoxylin and eosin. Slides were assessed by a pathologist blinded to the study groups and scored using a scoring system developed by Simons et al. (13) to grade the degree of lung injury. Briefly, lung injury was graded from 0 (normal) to 4 (severe) in four categories: interstitial inflammation, neutrophil infiltration, congestion, and edema. The total lung injury score was calculated by adding the individual scores for each category.

Immunohistochemistry

Formalin-fixed, paraffin-embedded lung tissue sections were cut into 4-μm thick sections. Then, the slides were deparaffinized in xylene, rehydrated in alcohol, and blocked for endogenous peroxidase using 3% hydrogen peroxide. Antigen retrieval was performed using 0.01 mol/L sodium citrate buffer (pH 6.0) through microwave processing and then tissue sections processed using the standard avidin-biotin-immunoperoxidase method. The slides were incubated in 10% normal goat serum for 30 min to prevent nonspecific staining. The sections were incubated for 2 h at room temperature with anti–rat ICAM-1 (CD54) monoclonal antibody (clone 1A29, diluted 1: 100; Endogen, Woburn, Mass). Thereafter, the sections were incubated with biotinylated secondary antibodies, followed by avidin-biotin peroxidase complexes for 30 min. We used 3-amino-9-ethylcarbazole substrate (LabVision, NeoMarkers, Fremont, Calif) as the chromogen and Mayer hematoxylin as the counterstain. For negative control, nonimmune serum was substituted for the primary antibody.

The ICAM-1 expression was evaluated semiquantitatively and graded as follows: 0, negative; 1+ baseline or endogenous; and 2+, strong and uniform in both alveolar capillaries and the large vessels of lung tissue. A pathologist reviewed the slides in a blinded fashion.

Statistics

All values were expressed as the mean ± SD. Data were compared by analysis of variance with post hoc analysis using Newman-Keuls test. When a difference was found, specific differences were identified by using Kruskal-Wallis test. Statistical evaluation was carried out by using SPSS 10.0 software (SPSS, Chicago, Ill). Values of $P < 0.05$ were accepted as significant.

RESULTS

Kaplan-Meier survival curves (Fig. 1) showed no mortality after the sham operation (survival 100%) and decreased survival to 38% in the control group ($P < 0.01$ vs. sham). Treatment with β-glucan significantly improved the survival rate to 63% throughout the 7-day observation period ($P < 0.05$). Administration of β-glucan with β-glucanase resulted in a decrease in the 7-day survival rate to 50% compared with the β-glucan group. Most of the lethality occurred within 3 days of surgery in septic animals.

As shown in Figure 2, plasma concentrations of TNF-α, IL-1β, and IL-6 were significantly elevated at the fifth hour

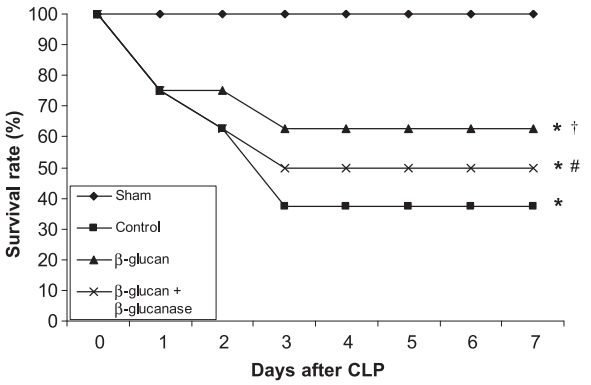

FIG. 1. **Effect of β-glucan treatment on survival.** The survival rate was estimated by the Kaplan-Meier method and compared by using log-rank test. *$P < 0.05$ vs sham group; †$P < 0.05$ vs control group; #$P > 0.05$ vs control group.

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after CLP in vehicle-treated rats ($P < 0.05$). When septic animals were treated with β-glucan, the levels of TNF-α, IL-1β, and IL-6 were markedly reduced ($P < 0.05$). Conversely, administration of β-1,3-D-glucanase suppressed the glucan-induced decrease in these cytokines.

We studied the neutrophil influx into lung tissue using the MPO activity determination. As shown in Figure 3, MPO levels significantly increased from 1.84 ± 0.26 U/g in the sham group of rats to 6.27 ± 2.45 U/g in control animals and to 5.46 ± 1.28 U/g in the rats treated with β-glucan plus β-glucanase. Rats treated with β-glucan alone had similar lung MPO activities to that observed in the sham-operated animals.

At the 18th hour, control animals demonstrated significantly more severe lung injury when compared with sham and β-glucan–treated animals ($P < 0.05$). The total lung injury score was 1.1 ± 0.3 in the β-glucan group and 1.9 ± 0.6 in the control group. Elimination of β-glucan with β-glucanase further increased the lung injury (2.2 ± 0.9). Lung specimens from control animals displayed significant histological changes including infiltration of numerous polymorphonuclear leukocytes and macrophages in the interstitial spaces, hemorrhage, and marked swelling of the alveolar walls. In contrast, these changes were attenuated in β-glucan–treated rats. The histological appearance of lung specimens from β-glucan–treated animals was similar to those of sham animals (Fig. 4).

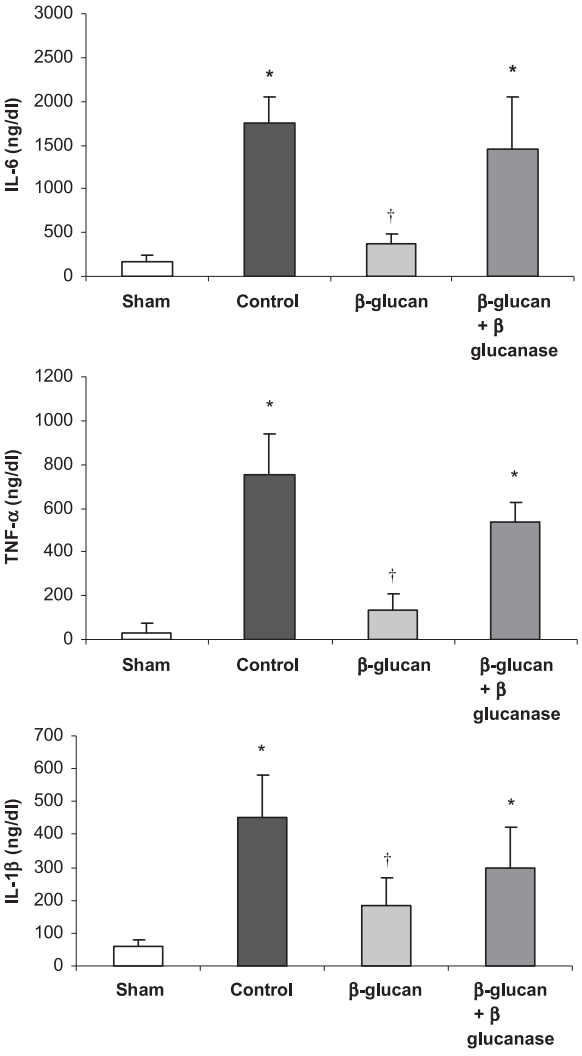

FIG. 2. **Plasma IL-6, TNF-α, and IL-1β concentrations in animals.** Polymicrobial sepsis was induced via CLP or sham operation. Plasma samples were collected 5 h thereafter, and IL-6, TNF-α, and IL-1β levels were determined by ELISA. Bar represents the mean ± SD. *$P < 0.05$ vs sham group; †$P < 0.05$ vs control and β-glucan + β-glucanase groups.

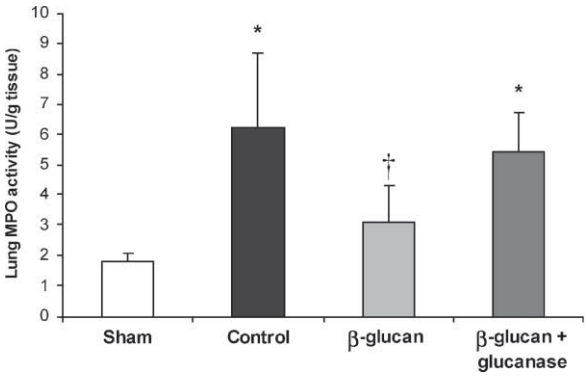

FIG. 3. **Effects of β-glucan treatment on CLP-induced lung neutrophil accumulation.** Lung MPO content was determined 18 h after CLP or sham operation. Bar represents the mean ± SD. *$P < 0.05$ vs sham group; †$P < 0.05$ vs control and β-glucan + β-glucanase groups.

Lung ICAM-1 is known to be involved in intrapulmonary recruitment of neutrophils, in a variety of conditions; we measured this adhesion molecule in lung tissue. As expected, ICAM-1 expression increased after the 18th hour of CLP (Fig. 5). Pretreatment of animals with β-glucan attenuated the expression of ICAM-1 caused by CLP in the lung tissues. However, the combination of β-glucan and β-glucanase noticeably increased ICAM-1 expression in response to CLP at 18 h.

DISCUSSION

The present study demonstrates that β-glucan, a clinically relevant nonspecific immunomodulator, can significantly attenuate the expression of proinflammatory cytokines and systemic inflammation in rat after sepsis. We have also shown that β-glucan can affect the lethality and the occurrence of acute lung injury as measured through end-organ histological damage in response to sepsis. The use of carbohydrate derivatives in the treatment of intra-abdominal sepsis is not new. Previous studies demonstrated a reduction in the mortality of severely injured patients receiving β-glucan therapy. In high-risk patients undergoing major thoracic or abdominal surgery, perioperative administration of PGG-glucan significantly decreases postoperative infection and mortality rates (9, 14). Tzianabos et al. (10) investigated the effects of two immunomodulator polysaccharides, PGG-(glucan and polysaccharide A (PSA)), on abscess formation and mortality in experimental intra-abdominal sepsis and reported their protective effects. We have previously shown the beneficial effects of β-glucan such as decreased weight loss, anastomotic leakage, and mortality in the setting of peritonitis (11). Although the protective effect of polysaccharides against peritonitis has been reported (9, 10, 15), little attention has been paid to investigate the effect of β-glucan on

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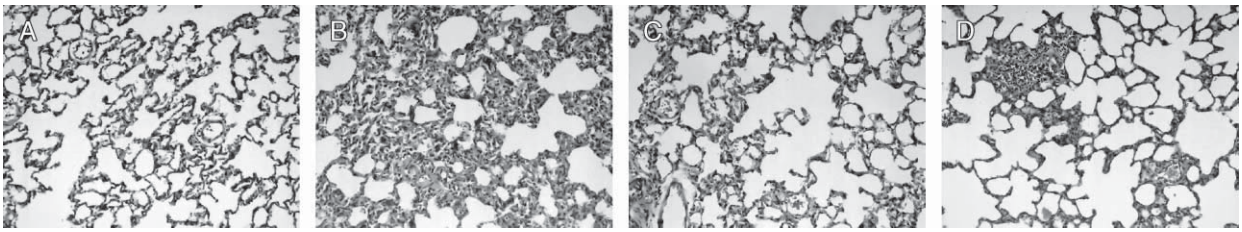

FIG. 4. **Effects of β-glucan treatment on lung histopathology.** Lungs were harvested at 18 h after septic shock and resuscitation and evaluated by a pathologist unaware of the groups the animals belonged to. Figure shows the normal appearance of lung specimens from sham animals (A) and the appearance of lungs from control animals (B). Note the marked inflammatory infiltrate, alveolar-capillary membrane thickening, and some areas of hemorrhage and alveolar edema. The histological appearance of lungs from β-glucan–treated animals (C) is shown. Note the similarity compared with sham animals (magnification ×200). The histological appearance of lungs from β-glucan + β-glucanase group (D) is also shown.

lung injury caused by bacterial sepsis (16). Moreover, the mechanism by which β-glucan exerts its protective effect against peritonitis is far from clear.

The site of infection (e.g., peritoneum) and the ability to contain it locally are critical in determining the severity of the septic syndrome and the likelihood of distant organ injury. Matute-Bello et al. (17) suggested a 3-compartment model to explain the host response to local infections. In this model, first compartment is the site at which bacteria enter the host and proliferate (e.g., the peritoneum), the second compartment includes the circulation and the reticuloendothelial system, and the third compartment includes remote organs. The lungs have been considered to be the remote organ system most commonly affected and the first to fail in peritonitis. A significantly high MPO activity after peritonitis may result from enhanced transmigration of neutrophils into lung tissues through the circulatory and reticuloendothelial system or a local release of neutrophils due to generalized infection (4, 18, 19). Furthermore, the activated neutrophils that infiltrate the lung produce proinflammatory cytokines, such as TNF-α and IL-1β, and play a key role in the development of acute lung injury by releasing neutrophil proteases and reactive oxygen species (2, 5). In the present study, the magnitude of neutrophil infiltration in lung was assessed by measuring the levels of MPO. There was a highly significant increase in MPO levels in lung after CLP-induced peritonitis which was attenuated by β-glucan. Downregulation of neutrophil infiltration by β-glucan is not specific for sepsis-induced lung injury. For example, glucan phosphate treatment attenuates burn-induced inflammation and increases resistance *Pseudomonas aeruginosa* burn wound infection in an experimental model of burn injury (20). Systemic application of β-glucan ameliorated pressure ulcer-induced oxidative organ injury and prevented neutrophil infiltration in the lung tissues (21). Moreover, several studies conducted in the past decade have shown that β-glucan reduced release of inflammatory cytokines, such as TNF-α, IL-1β, and IL-6 in other injury types (20, 22–24). We have demonstrated here that treatment of rats with β-glucan markedly attenuated the CLP-induced increase in plasma TNF-α, IL-1β, and IL-6 concentrations. In addition, β-glucanase blocked the effect of β-glucan. These findings, therefore, suggest that immunomodulation with β-glucan mediates the inhibition of the cytokine response, leading to a regression of neutrophilic lung inflammation.

The recruitment of circulating leukocytes to the sites of activated endothelium and subsequent pulmonary sequestration of leukocytes are pivotal in the pathogenesis of acute lung injury, including ARDS (2, 3, 25). Besides integrins and selectins, the cell adhesion molecules, ICAM-1 and vascular cell adhesion molecule (VCAM) 1, have been linked to leukocyte trafficking in various animal inflammation models (26). Monoclonal antibodies to ICAM-1 have been effective in decreasing pulmonary polymorphonuclear neutrophils accumulation in models of lung injury after hind-limb ischemia-reperfusion (27). Mice genetically deficient in ICAM-1 are resistant to septic shock induced by endotoxin (28). Moreover, enhanced pulmonary expression of ICAM-1 and increased circulating soluble forms of ICAM-1 have been found in septic patients, correlating with multiorgan failure and death (29, 30).

The blockade of adhesion molecules, which is thought to represent the final common pathway for adherence and margination of leukocytes to areas of inflammation and injury, has been targeted. In mice with lipopolysaccharide-induced shock, anti–VCAM-1 therapy attenuated by 60% neutrophils accumulation in liver and reduced hepatic necrosis

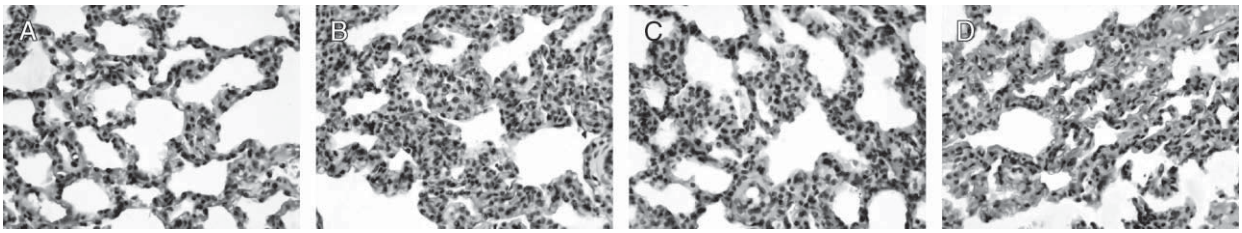

FIG. 5. **Representative sections of lung immunohistochemically stained for ICAM-1.** Control animals (B) showed increased lung ICAM-1 expression compared with sham (A) and β-glucan (C) groups. Note the increase in ICAM-1 expression in the β-glucan + β-glucanase group (D), as compared with the β-glucan–treated animals (magnification ×300).

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(31) However, VCAM-1 expression is often dissociated from neutrophils accumulation in experimental sepsis in mice (32). Laudes et al. (6) have recently demonstrated that the blockade of VCAM-1 did not reduce lung neutrophil accumulation as measured by MPO activity after CLP, but MPO levels declined when anti–ICAM-1 was administered to CLP mice. These data emphasize the importance of ICAM-1 pathway in neutrophil migration during sepsis. To explore the underlying mechanisms by which β-glucan achieves its beneficial effects, we investigated its influence on pulmonary ICAM-1 production. We demonstrated that β-glucan treatment decreases the expression of ICAM-1 in rat lung after CLP. We also found that β-glucan treatment reduces infiltration of neutrophils in lung tissues. Therefore, diminished expression of ICAM-1 in the lung by β-glucan provides a possible explanation for the decreased neutrophil infiltration and lung injury noted in our study. Furthermore, the coadministration of β-glucanase blocked the effect of the β-glucan, indicating the inhibition of ICAM-1 expression by β-glucan.

In conclusion, the current study provides evidence for increased expression of ICAM-1 during CLP-induced sepsis. All leukocytes use the β2-integrin/ICAM-1 interaction for adhesion and transmigration (26). Thus, the resulting accumulation of PMN in the lung is strongly dependent on increased ICAM-1 expression. Treatment with β-glucan, a clinically relevant nonspecific immunomodulator, markedly attenuated the expression of proinflammatory cytokines and systemic inflammation in rats with septic peritonitis. We have also shown that β-glucan can affect the lethality and the occurrence of acute lung injury as measured through end-organ histological damage in response to sepsis. It appears that the mechanism of β-glucan's effect on proinflammatory cytokine expression is by interfering with down-regulation of ICAM-1 and neutrophil accumulation pathways. We propose that β-glucan might be used as a therapeutic agent in the treatment of inflammatory lung injury related to sepsis.

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