EXPERIMENTAL STUDY

Protective effect of betaine against burn-induced pulmonary injury in rats

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ABSTRACT

BACKGROUND: This study was designed to determine possible protective effect of betaine treatment against oxidative injury in pulmonary tissue induced with thermal trauma.

METHODS: Under ether anesthesia, shaved dorsum of Wistar albino rats was exposed to a 90°C water bath for 10 seconds to induce burn injury. Betaine was administered orally (250 mg/kg) for a period of 21 days before burn injury, and single dose of betaine was administered after thermal injury. Control group rats were exposed to 25°C water bath for 10 seconds. Upon conclusion of experiment, rats were decapitated and blood was collected for analysis of pro-inflammatory cytokines and lactate dehydrogenase (LDH) activity. Lung tissue samples were taken to determine malondialdehyde (MDA) and glutathione (GSH) levels, myeloperoxidase (MPO), and N^{a+}/K^{+}-ATPase activity, in addition to histological analysis.

RESULTS: Burn injury caused significant increase in both cytokine levels and LDH activity. In lung samples, raised MDA levels, MPO activity, and reduced GSH levels and Na^{+}/K^{+}-ATPase activity were found due to burn injury.

CONCLUSION: Treatment of rats with betaine significantly restored GSH level and Na^{+}/K^{+}-ATPase activity, and decreased MDA level and MPO activity. According to the findings of the present study, betaine significantly diminishes burn-induced damage in tissue.

Keywords: Betaine; cytokines; lung injury; oxidative stress; thermal trauma.

INTRODUCTION

Thermal trauma is one of the most common problems faced in the emergency room. It may cause multiple organ injury distant from the burned area; therefore, morbidity and mortality is increased in thermal trauma patients.[1] In addition to direct tissue damage, inflammatory reactions and infection as major complications.[2]

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In thermal trauma patients, the lungs are the most affected organs as a result of the inflammatory process since the lungs produce inflammatory mediators and free oxygen radicals.[3] Several substances, including free oxygen radicals, vasodilators, and chemical mediators, activate pneumocytes. These substances pass through systemic blood and increase the inflammatory response, which causes edema, surfactant alterations, bronchial obstruction, and hypoxia, as well as development of systemic inflammatory response syndrome (SIRS) in patients with burns.[3,4]

Betaine is a natural chemical compound found in several foods such as wheat, shellfish, spinach, and sugar beets.[5] The first effect of betaine molecule, as an osmolyte, is to protect cells, proteins, and enzymes under osmotic stress conditions, drought, high salinity, or high temperature. Betaine also acts as a methyl donor in many biological pathways.[6] It has been demonstrated in studies that betaine prevented membrane

stabilization in tissue by restoring both non-enzymatic and enzymatic antioxidants, and that it had a protective effect on mitochondrial function, lipid metabolism, and antioxidant defense system in experimentally induced myocardial infarction in Wistar rats.[7–11]

Neutrophil infiltration is known as the source of free oxygen radicals causing afterburn injury, as well as being responsible for local and distant injury.[12] Various mediators and cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin 1 beta (IL-1β), play important roles in major complications of burn injury. Betaine also modulates immune functions of liver macrophages under osmotic stress through TNF-α release, phagocytosis, depression of prostaglandin synthesis, and cyclooxygenase-2 (COX-2) expression.[13]

In light of these findings, the present study was designed to investigate whether and to what extent betaine would provide protection against burn-induced tissue damage by determining the presence of oxidative tissue injury using biochemical and histological parameters.

MATERIALS AND METHODS

Animals

Wistar albino rats of both sexes weighing 200 to 250 g were obtained from Marmara University School of Medicine Animal Facility. The rats were kept at a constant temperature (22±1°C) with 50% humidity, 12-hour light and dark cycles, and fed with standard rat chow until 12 hours before the experiment without restriction of access to water. All experimental protocols were approved by the Marmara University Animal Care and Use Committee (33.2010.mar).

Thermal Injury and Experimental Design

Rats were divided into 3 groups: control, burn, and betaine-treated burn group. Each group consisted of 6 rats. For a second-degree burn involving 30% of total body surface area, dorsum of rats was shaved and subsequently exposed to 90°C water bath for 10 seconds while under brief ether anesthesia.[14] This second-degree burn method was chosen to investigate the effects of betaine on partial-thickness burn damage. Animals were then resuscitated with 10 mL/kg subcutaneous infusion of physiological saline solution to hind limb. Betaine (Lily's) was administered orally (250 mg/kg) for a period of 21 days before thermal injury and single dose of betaine was administered after burn. In both saline- and betaine-treated burn groups, rats were decapitated at 24 hours following burn injury. In order to rule out the effects of anesthesia, same protocol was used with control group, except that dorsum was dipped in 25°C water bath for 10 seconds.

After decapitation, blood was collected to assay pro-inflammatory cytokines (TNF-α and IL-1β) and lactate dehydrogenase (LDH) activity.

In order to evaluate presence of oxidant injury in the organ (lung), tissue samples were taken and stored at -80°C in order to determine malondialdehyde (MDA) and glutathione (GSH) levels, and myeloperoxidase (MPO) and Na^+/K^+-ATPase activity.

Tissue samples were fixed in 10% (v/v) buffered p-formaldehyde and prepared for routine parafin embedding for histological analysis. Tissue sections (6 µm) were stained with hematoxylin and eosin (H&E) and examined under a light microscope (Olympus-BH-2; Olympus Corporation, Tokyo, Japan). An expert histologist who was unaware of the treatment group properties performed histological assessments.

Cytokine Assay

TNF-α and IL-1β were analyzed based on manufacturer's instructions and guidelines using enzyme-linked immunosorbent assay (ELISA) kits (Biosource International, Nivelles, Belgium) specifically for plasma levels of rat cytokines. These kits were selected based on high degree of sensitivity and specificity, interassay and intraassay precision, and small amount of plasma sample required to conduct assay. Serum LDH levels were determined spectrophotometrically using an automated analyzer.[15]

Malondialdehyde and Glutathione Assays

To determine MDA and GSH levels, samples of tissue were homogenized with ice-cold 150 mM KCl. As described by Beuge et al.,[16] MDA levels were assayed by monitoring formation of thiobarbituric acid reactive substances (TBARS), products of lipid peroxidation. Lipid peroxidation was expressed in terms of MDA equivalents using an extinction coefficient of $1.56 \times 10^5\ M^{-1}\ cm^{-1}$ and results are expressed as nmol MDA/g tissue. GSH measurements were performed with modification of Ellman procedure.[17] After centrifugation at 1077 × g for 10 min, 0.5 mL supernatant was added to 2 mL of 0.3 mol/L $Na_2HPO_4.2H_2O$ solution. A 0.2 mL solution of dithiobisnitrobenzoate (0.4 mg/mL 1% sodium citrate) was added and absorbance at 412 nm was measured immediately after mixing. GSH levels were calculated using an extinction coefficient of $1.36 \times 10^4\ M^{-1}\ cm.^{-1}$ Results are expressed in µmol GSH/g tissue.

Myeloperoxidase Activity

MPO is an enzyme found predominantly in the azurophilic granules of polymorphonuclear neutrophils (PMN). Tissue MPO activity is frequently utilized to estimate tissue PMN accumulation in inflamed tissue and correlates significantly with the number of PMN histochemically determined in tissue.

MPO activity was measured in tissue using procedure similar to that documented by Hillegass.[18] Tissue samples were homogenized in 50 mM potassium phosphate buffer (PB, pH 6.0), and centrifuged at 41400 × g (10 min); pellets were suspended in 50 mM PB containing 0.5% hexadecyltrimethylam-

monium bromide (HETAB). After 3 freeze and melt cycles, with sonication between cycles, samples were centrifuged at 41400 × g for 10 min. Aliquots (0.3 mL) were added to 2.3 mL of reaction mixture containing 50 mM PB, o-dianisidine and 20 mM H_2O_2 solution. One unit of enzyme activity was defined as amount of MPO present that caused change in absorbance measured at 460 nm for 3 minutes. MPO activity is expressed as U/g tissue.

Na^+/K^+-ATPase Activity

Since activity of Na^+/K^+-ATPase, a membrane-bound enzyme required for cellular transport, is very sensitive to free radical reactions and lipid peroxidation, reductions in activity can indicate membrane damage indirectly. Measurement of Na^+/K^+-ATPase activity is based on measurement of inorganic phosphate released by ATP hydrolysis during incubation of homogenates with an appropriate medium containing 3 mM ATP as substrate. Total ATPase activity was determined in presence of 100 mM NaCl, 5 mM KCl, 6 mM $MgCl_2$, 0.1 mM ethylenediaminetetraacetic acid (EDTA), 30 mM Tris HCl (pH 7.4), while Mg^{2+}-ATPase activity was determined in the presence of 1mM ouabain. Difference between total and Mg^{2+}-ATPase activities was taken as a measure of Na^+/K^+-ATPase activity.[19] Reaction was initiated with addition of homogenate (0.1 mL), and 5-minute pre-incubation period at 37° C was allowed. Following addition of Na_2ATP and a 10-minute re-incubation period, reaction was terminated with addition of ice-cold 6% perchloric acid. Mixture was then centrifuged at 3500 g, and Pi in the supernatant fraction was determined with Fiske and Subbarow method.[20] Specific activity of enzyme was expressed as nmol Pi mg^{-1} protein h^{-1}. Protein concentration of supernatant was measured with Lowry method.[21]

Histopathological Analysis

For light microscopic investigations, lung specimens were fixed in 10% buffered formalin for 48 hours, dehydrated in ascending alcohol series, and embedded in paraffin wax. Approximately 5-µm-thick sections were stained with H&E for general morphology. Histological assessments were made with a photomicroscope (Olympus BX 51; Olympus Corporation, Tokyo, Japan) by an experienced histologist who was unaware of experimental groups and each group was described in detail.

Statistical Analysis

Statistical analysis was carried out using GraphPad software (Prism 3.0; GraphPad Software, San Diego, CA, USA). All data were expressed as means±SEM. Groups of data were compared with analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. Values of $p<0.05$ were regarded as significant.

RESULTS

As shown in Table 1, Serum LDH activity and plasma levels of pro-inflammatory cytokines (TNF-α, IL-1β) in burn group were significantly higher ($p<0.001$) than those of control group, and betaine treatment significantly reduced the elevations ($p<0.001$).

In accordance with these findings, level of the major cellular antioxidant GSH in vehicle-treated burn group was depleted ($p<0.001$); however, in betaine-treated burn group, depleted GSH stores were partially replenished with this antioxidant ($p<0.05$; Fig. 1a). MDA level, measured as major degradation product of lipid peroxidation in lung tissue, was found to be significantly higher in burn group ($p<0.01$) compared to that of control group, while treatment with betaine reduced elevation ($p<0.05$; Fig. 1b).

MPO activity, accepted as an indicator of neutrophil infiltration, was significantly higher in lung tissue of burn group treated with vehicle ($p<0.01$) than that of control group (Fig. 2a). Activity of Na^+/K^+-ATPase, indicating functional transport capacity of lung cells, was found to be significantly decreased in burn group compared to control group ($p<0.001$); however, betaine treatment significantly reduced burn-induced decrease in lung Na^+/K^+-ATPase activity ($p<0.05$; Fig. 2b).

In control group, alveolar structure and interstitial space were found to be regular (Fig. 3a). In burn group, severe inflammation, congestion, and alveolar volume decrease due to edema of interstitial space were found in burned lung tissue, and erythrocytes were observed inside alveoli and part of alveolar wall (Fig. 3b). In the betaine-treated burn group, regression of inflammation and congestion were found, as well as decrease in interstitial edema (Fig. 3c).

Table 1. Serum lactate dehydrogenase (LDH) activity (U/l), tumor necrosis factor-alpha (TNF-α) and interleukin 1 beta (IL-1β) levels of control, vehicle-treated, and betaine-treated burn groups. For each group, n=6

	Control	Burn	Burn-Betaine
Lactate dehydrogenase	1383±134	2373±165***	1480±109^{+++}
TNF-α	8.12±1.03	43.06±5.12***	15.08±2.08^{+++}
IL-1β	16.22±1.52	68.28±4.08***	33.25±6.98^{+++}

$^{***}p<0.001$, compared to control group; $^{+++}p<0.01$, compared to betaine-treated burn group.

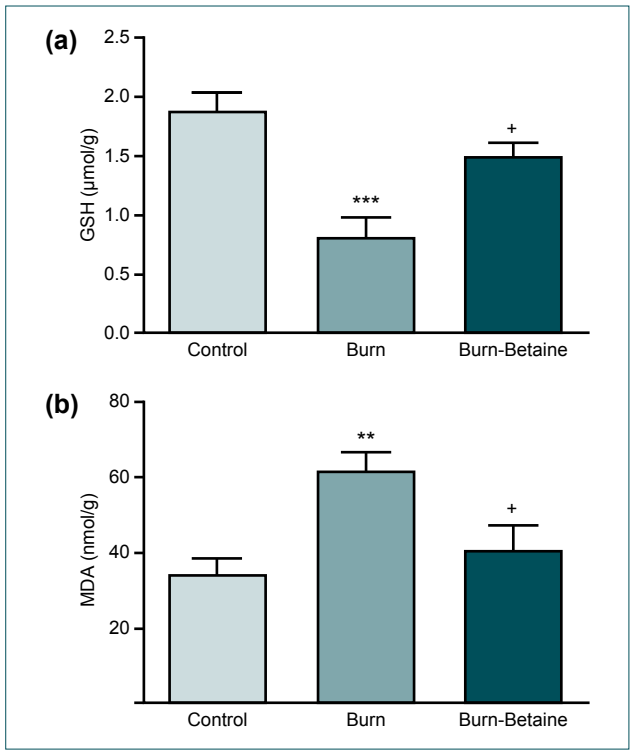

Figure 1. (a) Glutathione (GSH), **(b)** malondialdehyde (MDA) level in lung tissue of control, vehicle-treated burn, and betaine-treated burn groups. Each group consisted of 6 animals. **p<0.01; ***p<0.001, compared to control group; +p<0.05, compared to vehicle-treated burn group.

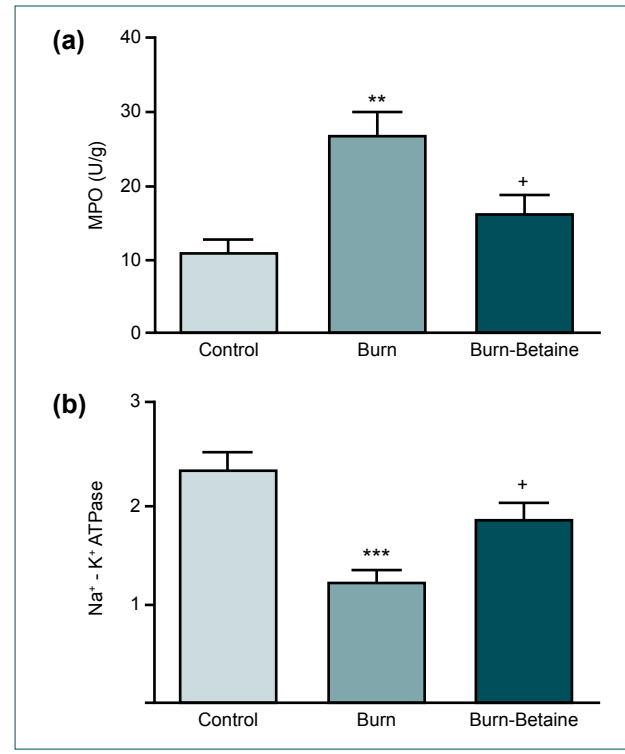

Figure 2. (a) Myeloperoxidase (MPO), **(b)** Na+/K+-ATPase activity in lung tissue of control, vehicle-treated burn, and betaine-treated burn groups. Each group consisted of 6 animals. **p<0.01; ***p<0.001, compared to control group; +p<0.05, compared to vehicle-treated burn group.

DISCUSSION

Burns generated in the present study led to significant increases in lipid peroxidation and MPO activity, along with decreased GSH level and Na^+/K^+-ATPase activity in lung tissue, and elevated serum level of LDH and pro-inflammatory mediators TNF-α, and IL-1β, demonstrating presence of systemic oxidative injury due to thermal injury. Betaine administration protected against systemic oxidative injury and limited tissue damage.

Studies have shown that betaine prevents membrane stabilization in tissue by restoring both non-enzymatic and enzymatic antioxidants, and that it has a protective effect on mitochondrial function, lipid metabolism, and antioxidant defense system in experimentally induced myocardial infarction in Wistar rats.[7–11]

Thermal injury model is most preferred experimental study method with regard to burns. Distant organ injury caused by burns is a clinical situation triggered by inflammatory reaction. After thermal trauma, there is a complex relationship between tissue types and several immunoregulator systems such as arachidonic acid/prostaglandin pathway, complement pathways, cytokine network, neuroendocrine, and metabolic regulatory system.[22,23] Release of pro-inflammatory mediators such as IL-1β, IL-6, and TNF-α is factor in immune dysfunction. In the present study, it was observed that TNF-α and IL-1β levels were significantly elevated after burn injury.

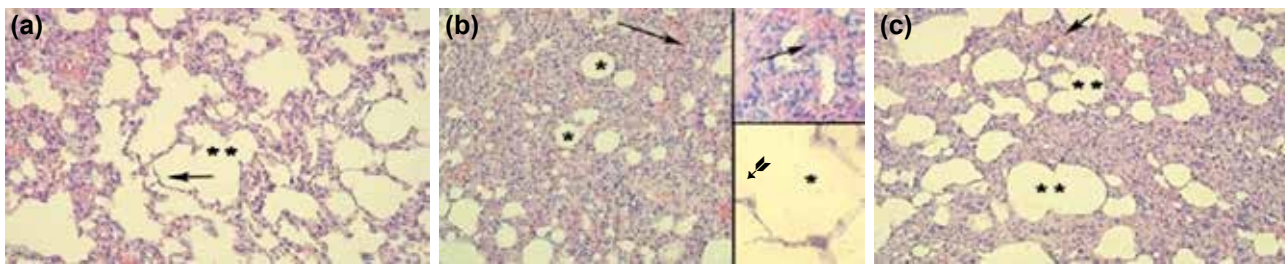

Figure 3. (a) The control group: (**) regular alveolar structure and interstitial space, (□) alveolary epitelium. **(b)** The burn group: (□) severe inflammation, congestion, and (*) alveolar volume decrease (➵) erythrocytes inside alveoli. **(c)** The betaine treated burn group: (**) regression of inflammation and congestion, (□) mild interstitial edema. (HE x200; insets x400).

[24,25] In betaine-treated burn injury group, levels of cytokines were suppressed, indicating that betaine has an important role in pro-inflammatory cytokine levels in blood. Therefore, agents such as betaine could be helpful in preventing tissue oxidation and could improve success of burn treatment. Other studies have also determined that betaine has an inhibitory effect on cytokines.[26,27]

Another indicator for tissue injury is alteration of LDH level.[28] In their study, Wettstein and Häussinger showed that betaine decreased LDH level on perfused rat liver after ischemia and reperfusion through its cytoprotective effect.[29] In the present study, LDH level of rats with thermal injury was found to be high; however, in betaine-treated group it was significantly lower.

Study results have indicated that increased MDA level is related to oxidative injury caused by thermal trauma.[30] Kanbak et al. reported that betaine has cytoprotective effect, decreasing MDA level and countering cytotoxic effect of free radicals caused by chronic ethanol administration to pancreas tissues.[31]

In the current study, MDA level in lung tissue increased. This increase was related to lipid peroxidation, which correlates with previous studies and supports role of free radicals in burn-induced injury.[32] In betaine-treated group, increased MDA level caused by injury was significantly decreased.

GSH protects cell against oxidative injury by reacting with free radicals and peroxidate.[28] In the present study, lung tissue structure was damaged by burn due to oxidative stress. Other studies have also shown that GSH level in lung tissue significantly decreased with betaine treatment after burn,[22,28,33] as was the case in current study. Antioxidant therapy is now used in several pathological conditions with oxidant stress, and results have been positive.[28] Kim and Kim showed that for hepatotoxicity caused by chloroform, betaine increased plasma and liver glutathione levels through its effect on transsulfuration pathway in liver.[34] In the present study, betaine applied after burn helped significantly reduce GSH level in lung tissue.

Neutrophils are responsible for tissue injury distant from burn area, and activated neutrophils release MPO enzyme. Betaine inhibits neutrophil infiltration and prevents tissue injury due to MPO activity.[12] Present study data indicated that MPO activity in lung tissue elevated by burn decreased with betaine treatment.

Na^+/K^+-ATPase is membrane-bound enzyme responsible for active transport of several ions in the cell membrane. Local or systemic tissue Na^+/K^+-ATPase activity is inhibited in case of thermal injury by effect of free radicals.[22] As seen in the literature, in present study, Na^+/K^+-ATPase activity significantly decreased in burn group and increased in treatment group. In one study, antioxidant effect of betaine was examined in rats given gastric defect as result of consuming HCl-ethanol. Betaine reduced free radicals, DNA, lipid, and protein damage caused by HCl-ethanol. Oral betaine administration preserved structure and function of membrane, and had protective effect against lipid peroxidation and protein carbonyl function caused by reactive oxidants.[33] These findings suggest that betaine inhibits free radicals and lipid peroxidation, and therefore Na^+/K^+-ATPase activity is decreased.

This experimental thermal burn model led to increase in pro-inflammatory blood cytokines, decrease in antioxidant balance caused by neutrophil activation, increase in free radical levels, and tissue injury because of the lipid peroxidation. These results caused tissue injury not only in the burn area, but also in distant organs.

Findings indicate that betaine possesses neutrophil-dependent, anti-inflammatory effect that prevents burn-induced damage in tissue and protects against oxidative organ damage. Use of betaine could be helpful to improve quality of life and recovery of patients with burn-induced lung injury.

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Conflict of interest: None declared.

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DENEYSEL ÇALIŞMA - *ÖZET*

Sıçanlarda yanığa bağlı olarak gelişen akciğer hasarına karşı betain'in koruyucu etkisi

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AMAÇ: Bu çalışma, yanığa bağlı olarak gelişen akciğerdeki oksidatif hasara karşı betain tedavisinin olası koruyucu etkisini tanımlamak için tasarlandı.
GEREÇ VE YÖNTEM: Yanık oluşturmak için sırt derileri traş edilmiş Wistar albino türü sıçanlar, eter anestezisi altında 10 saniye süreyle 90°C suya tutuldu. Yanık oluşturulmadan evvel 21 gün süre ile betain 250 mg/kg dozunda oral olarak uygulandı ve yanık oluşturulduktan sonra tek doz betain uygulaması yapıldı. Kontrol grubunda ise aynı işlem uygulandıktan sonra sırt bölgeleri 10 saniye süreyle 25°C suya tutuldu. Deney sonunda sıçanlar dekapite edildi ve kan numuneleri proinflamatuvar sitokinleri (tümör nekroz faktör- [TNF-] and interlökin 1 beta [İİL-1]) ve LDH aktivitesini analiz etmek için toplandı. Akciğer doku örnekleri histolojik analizlerin yanı sıra MDA ve GSH seviyelerini, MPO ve Na^+, K^+-ATPaz aktivitesini belirlemek için alındı.
BULGULAR: Yanık hasarı sitokin seviyelerinde ve LDH aktivitesinde önemli derecede artışa neden oldu. Yanık hasarına bağlı olarak akciğer dokularında MDA seviyeleri ve MPO aktivitesi yüksek, GSH seviyeleri ile Na^+, K^+-ATPaz aktivitesi düşük bulundu.
TARTIŞMA: Bu çalışmanın bulgularına göre yanığın serum ve dokuda neden olduğu hasarın betain ile anlamlı olarak azaldığı saptanmıştır.
Anahtar sözcükler: Akciğer hasarı; betain; oksidatif stres; sitokinler; termal travma.

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