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ORIGINAL ARTICLE

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Poly (adp-ribose) synthetase inhibition reduces oxidative and nitrosative organ damage after thermal injury

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Abstract Poly (ADP-ribose) synthetase (PARS) is a nuclear enzyme activated by DNA single-strand breakage, which can be triggered by reactive oxygen and nitrogen species. Activation of this enzyme depletes the intracellular concentration of energetic substrates such as nicotinamide adenine dinucleotide (NAD). Eventually, this process results in cell dysfunction and cell death. PARS inhibitors have successfully shown benefits in several experimental models of ischemia-reperfusion injury, inflammation, and sepsis. In our experimental study, we investigated the role of 3-aminobenzamide (3-AB), a nonspecific PARS inhibitor, in systemic organ damage after burn. Twenty-four Wistar rats were randomly divided into three groups. The sham group ($n=8$) was exposed to 21°C water, and the burn group ($n=8$) and the burn-plus-3-AB group ($n=8$) were exposed to boiling water for 12 s to produce a full-thickness burn of 35–40% of total body surface area. In the burn-plus-3-AB group, 3-AB 10 mg/kg was given intraperitoneally 10 min before thermal injury. Twenty-four hours later, tissue samples were obtained for biochemical analysis from lung, intestine, and kidney. In the burn group, tissue malondialdehyde, myeloperoxidase, and 3-nitrotyrosine levels in all organs were significantly increased compared with the sham group ($p<0.05$). Pretreatment with 3-AB significantly reduced burn-induced organ damage ($p<0.05$). These data provide evidence of the relationship between the PARS pathway and lipid peroxidation in systemic organ damage after thermal injury.

Keywords Poly (adp-ribose) synthetase · Thermal injury · Oxidative organ damage · Nitrosative organ damage · 3-aminobenzamide

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Introduction

Despite recent advances in the management of burn care, systemic inflammatory response syndrome and multiple organ failure still continue to be leading causes of morbidity and mortality [1, 2]. Thermal injury is accompanied by complex events that exert deleterious effects on various organs in different systems distant from the original burn wound. Although the pathophysiological basis of organ damage remains unclear, there is increasing evidence that both oxidative and nitrosative stress have important roles in the development of multiple organ failure after thermal injury [3–5].

Following burn injury, all tissues are subjected to ischemia, and consequently, especially during burn resuscitation, reperfusion injury occurs [4, 6]. Recent studies have suggested that oxidative and nitrosative stress initiate an inflammatory cascade that includes acute phase protein synthesis, upregulation of inflammatory adhesion molecules, and proinflammatory cytokine release [7, 8]. Thus, tissue or organ injury after thermal trauma appears to be mediated both by reactive oxygen species (ROS) and reactive nitrogen species (RNS) such as hydroxyl radical, superoxide anion, hydrogen peroxide, and peroxynitrite. It has been shown that burn injury is associated with lipid peroxidation mediated by ROS and is believed to be an important cause of oxidative damage to cellular membranes and, eventually, cell death [9].

Recently, it has been demonstrated that nitric oxide (NO) plays a crucial role in cellular injury in burns. Burn

trauma produces a significant upregulation of the inducible nitric oxide synthetase (iNOS); consequently, iNOS-mediated nitric oxide production is upregulated. This overabundance of NO produces significant cellular toxicity via several mechanisms [10].

The toxicity of NO has been attributed to peroxynitrite ($ONOO^-$), which is formed by reaction of NO with superoxide anion [11]. Peroxynitrite reacts with cellular lipid and protein components, consequently disturbing their function. Another pathway of cell death triggered by peroxynitrite leads to the loss of cellular energy via the induction of DNA single-strand breaks and subsequent activation of the nuclear enzyme poly (ADP-ribose) synthetase (PARS) [12]. The PARS activation, which is most likely due to peroxynitrite production, depletes the intracellular concentration of energetic substrate, nicotinamide dinucleotide (NAD), thus leading to cellular dysfunction and cell death [7]. Pharmacological inhibition of PARS has been shown to have beneficial effects against peroxynitrite-mediated cell injury [13]. Nowadays, beneficial effects of PARS inhibition have been reported in many experimental models such as ischemia-reperfusion injury and sepsis. However, we found no published data on PARS inhibition in different systems after burn injury. Therefore, in this study we aimed to investigate the role of PARS inhibition on organ damage after thermal injury.

Materials and methods

The experimental procedures performed in this study were in concordance with the guidelines of the Turkish National Institutes of Health. The experimental protocol was approved by the Ethical Committee of Mersin University. Wistar rats weighing between 200 and 250 g were used in this study. The rats were housed at constant temperature with 12-h periods of light-dark exposure. The animals were allowed to access to standard rat chow and water ad libitum. A 1-week acclimatization period was used.

Experimental design

After the stabilization period, 24 rats were randomly divided into three groups. The first group (sham group, $n = 8$) was exposed to 21°C water 10 min after saline injection (1 ml/100 g intraperitoneally). The second group (burn group, $n = 8$) was exposed to thermal injury and given an intraperitoneal saline injection 10 min before thermal injury (1 ml/100 g). The third group (burn-plus-3-AB group, $n = 8$) received thermal injury 10 min after an intraperitoneal injection of 3-AB (10 mg/kg; A-0788, Sigma, USA). All animals were sacrificed 24 h after thermal injury. A midline laparotomy was performed, and samples of ileum, kidney, and lung were harvested for biochemical evaluation.

Thermal injury

Animals were anesthetized with intramuscular injections of ketamine hydrochloride (50 mg/kg) and morphine sulphate (15 mg/kg). The burn model described by Walker and Mason was used in this study [14]. The animals' backs were shaved to allow direct skin contact between skin and hot water. Next, a corresponding metal template immersed in boiling water for 12 s was applied to produce a full-thickness burn. The total area of the burn was 30–35% of the rat's total body surface. The rats in the sham group were exposed in an identical setting, except that room-temperature water (21°C) was used instead of boiling water. All animals in the burn and the burn-plus-3-AB groups were resuscitated with intraperitoneal injections of 2 ml/100 g saline following burn injury and were allowed water and standard rat chow after recovering from anesthesia. No animals died within the first 24 h of the postburn period.

Detection of MDA levels

One part of the tissue was homogenized in 10 parts 15 mmol/l KCL for malondialdehyde (MDA) assay. MDA is an end-product of fatty acid peroxidation that reacts with thiobarbituric acid (TBA) to form a colored complex. Measurement of MDA content by TBA reactivity is the most widely used method for assessing lipid peroxidation [15]. The principle of the method is based on measuring absorbance of the pink color produced by the interaction of TBA with MDA at 530 nm. Values were expressed as nmol/g wet tissue weight.

Measurement of tissue myeloperoxidase (MPO) activity

One part of the tissue was homogenized in 10 parts HETAAB buffer for myeloperoxidase (MPO) activity assay. The determination of tissue MPO activity depends on the fact that it reduces dimethoxybenzidine. Ileal segments were homogenized in 0.5% hexadecyltrimethylammonium bromide in 10 nM 3-(N-morpholino) propane sulfonic acid and centrifuged at 15,000 g for 40 min. An aliquot of supernatant was mixed with a solution of 1% (w/v) dimethoxybenzidine and 1 nM hydrogen peroxide. After 30 min of incubation, the reaction was stopped by adding 3 M HCl. Activity was measured spectrophotometrically as the change in absorbance at 410 nm at 37°C [16]. Results are expressed as units of MPO activity per gram of tissue.

3-nitrotyrosine detection

3-nitrotyrosine (3-NT) and tyrosine were obtained from Sigma Chemical (St. Louis, USA). H_2O_2, sodium acetate, citrate, NAOH, MnO_2, H_3PO_4, KH_2PO_4, and K_2HPO_4 were purchased from Merck Chemical

(Deisenhofen, Germany). All organic solvents were HPLC grade. The tissues were homogenized in ice-cold phosphate-buffered saline (pH 7.4). Equivalent amounts of each samples were hydrolyzed in 6 N HCl at 100°C for 18–24 h, and samples were then analyzed on an Agilent 1100 HPLC apparatus. The analytical column was a 5-μm pore size Spherisorb ODS-2 C_{18} reverse-phase column (4.6×250 mm; HiChrom, Reading, UK). The mobile phase was 50 mmol/l sodium acetate/50 mmol/l citrate/8% (v/v) methanol, pH 3.1. HPLC analysis was performed under isocratic conditions at a flow rate of 1 ml/min and UV detector set at 274 nm. 3-NT peaks were determined according to retention time, and the peaks were confirmed either by spiking with added exogenous 3-NT (10 μmol/l) or reducing to aminotyrosine [17]. 3-NT levels were expressed as nmol 3-NT/μmol tyrosine.

Statistical analysis

Statistical analysis for proportional comparisons of biochemical values was done using one-way ANOVA followed by Bonferroni's multiple comparisons tests. All data are presented as mean ± SD; p-values < 0.05 were considered statistically significant.

Results

All animals survived the experimental protocol. The results of the tissue biochemical analysis are presented in Table 1.

Myeloperoxidase activity

Tissue MPO activity significantly increased in the lung, kidney, and ileum in the thermal injury groups compared with the sham group ($p < 0.05$). PARS inhibition with 3-AB significantly decreased MPO activity in all tissues compared with the burn group ($p < 0.05$; Fig. 1).

Malondialdehyde levels

In all groups, MDA tissue levels correlated with MPO activity. In the burn group, MDA levels of lung, kidney, and ileal tissue were found to be significantly increased, whereas 3-AB caused a decrease in MDA levels in all tissues ($p < 0.05$; Fig. 2).

3-nitrotyrosine levels

3-NT levels in tissues are demonstrated in Fig. 3. Thermal injury caused significant increase in 3-NT levels in the lung, kidney, and ileum in the burn group compared with the sham group ($p < 0.05$), and 3-AB administration reversed these elevations ($p < 0.05$).

Discussion

The results of the present study demonstrate that PARS inhibition reduces postburn oxidative and nitrosative systemic organ damage as evidenced by changes in MDA and 3-NT levels and MPO activity. These findings suggest a relationship between the PARS pathway and the oxidative and nitrosative stress of burn-induced organ damage.

Thermal injury of the skin results both in local tissue damage and a systemic inflammatory response that is extremely complex, resulting in local burn tissue injury as well as systemic effects involving organs distant from the burn area itself [3, 4]. Experimental and clinical studies have shown that a local burn insult produces oxidant-induced organ changes as evidenced by increased lipid peroxidation in different organs such as intestine, liver, lung, and kidney [18, 19]. Lipid peroxidation, mediated by ROS, is believed to be an important cause of oxidative damage to cellular membranes and, eventually, cell death in burn injury [4]. However, RNS such as nitric oxide and peroxynitrite also play an important role in lipid peroxidation after thermal injury [10]. As a strong oxidative and nitrosative mediator, $ONOO^-$, the ugly face of NO [20], can cause cellular damage via several pathways. For example, most of the antioxidant enzymes such as superoxide dismutase and catalase can be inactivated by peroxynitrite [21]. Moreover, $ONOO^-$ directly causes lipid peroxidation on many cellular membranes, thereby disturbing their functions [22]. In our study, we observed that the level of tissue MDA, which is the product of lipid peroxidation, was significantly increased in lung, intestine, and kidney after thermal injury. This result shows that it may lead to

Table 1 Results of biochemical analysis of tissue samples (values expressed as mean ± SD; *MDA* malondialdehyde, *MPO* myeloperoxidase, *3-NT* 3-nitrotyrosine)

	Sham			Burn[a]			Burn-plus-3-AB		
	MDA	MPO	3-NT	MDA	MPO	3-NT	MDA	MPO	3-NT
Lung	15.54 ± 3.6	0.1081 ± 0.011	17.09 ± 2.2	27.88 ± 6.6	0.2166 ± 0.028	28.11 ± 5.5	18.73 ± 6.1	0.1235 ± 0.013	18.3 ± 3.3
Kidney	11.56 ± 3.3	0.1467 ± 0.046	18.58 ± 4.6	24.87 ± 4.09	0.2329 ± 0.024	27.8 ± 7.6	12.49 ± 2.8	0.1716 ± 0.021	19.6 ± 2.3
Ileum	12.85 ± 4.8	0.1709 ± 0.027	30.7 ± 3.3	22.96 ± 6.3	0.3003 ± 0.03	41.8 ± 8.07	14.75 ± 2.8	0.17 ± 0.028	30.6 ± 3.9

[a] $p < 0.05$, significantly different from the other groups

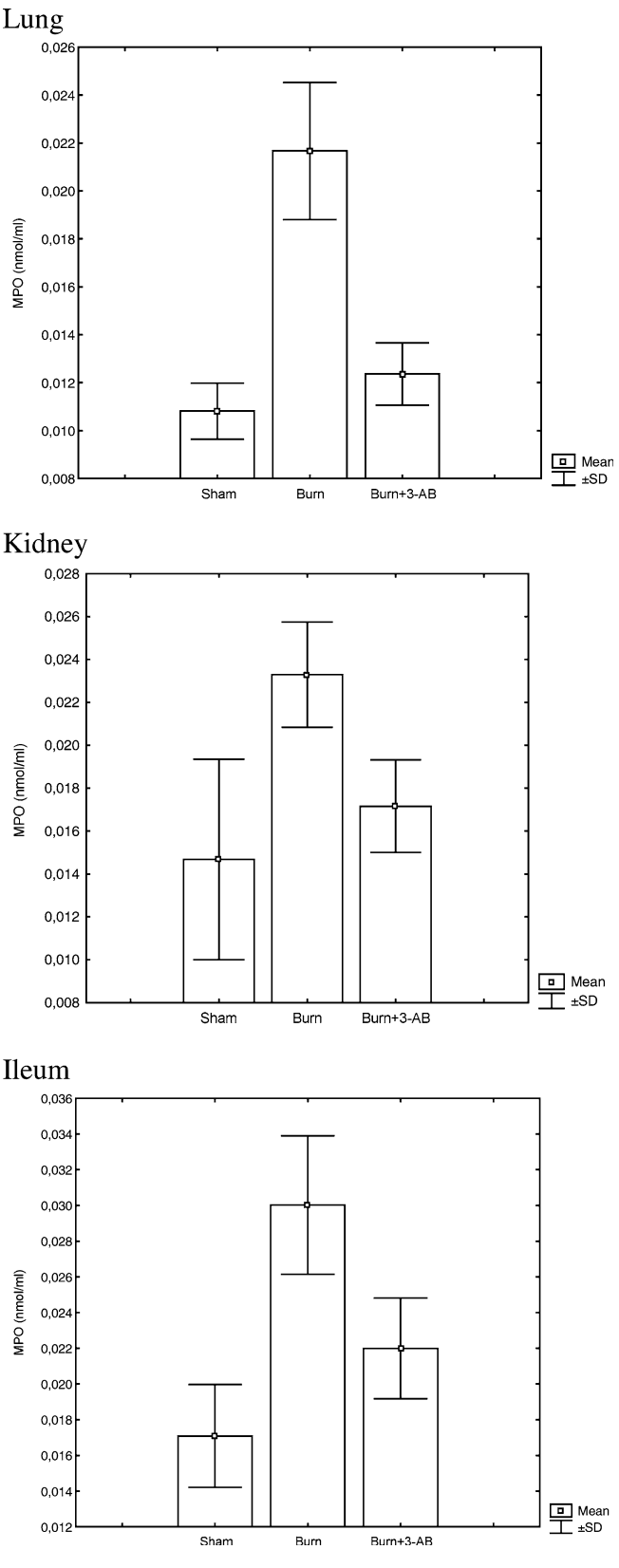

Fig. 1 Myeloperoxidase (MPO) activities in lung, kidney, and ileum in all groups. Data are expressed as mean ± SD. MPO activities in the burn group were significantly different from those in the other groups ($p < 0.05$)

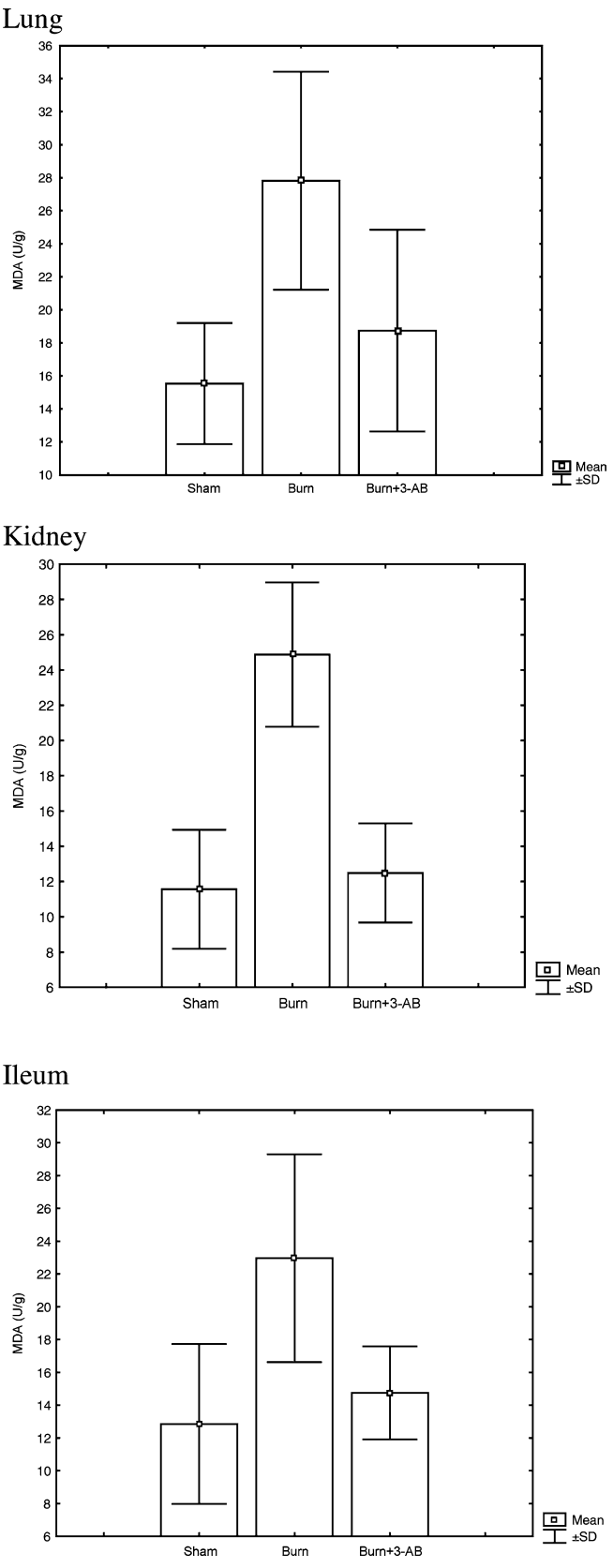

Fig. 2 Malondialdehyde (MDA) levels in lung, kidney, and ileum in all groups. All data are presented as mean ± SD. MDA levels in the burn group were significantly increased compared with the other groups ($p < 0.05$)

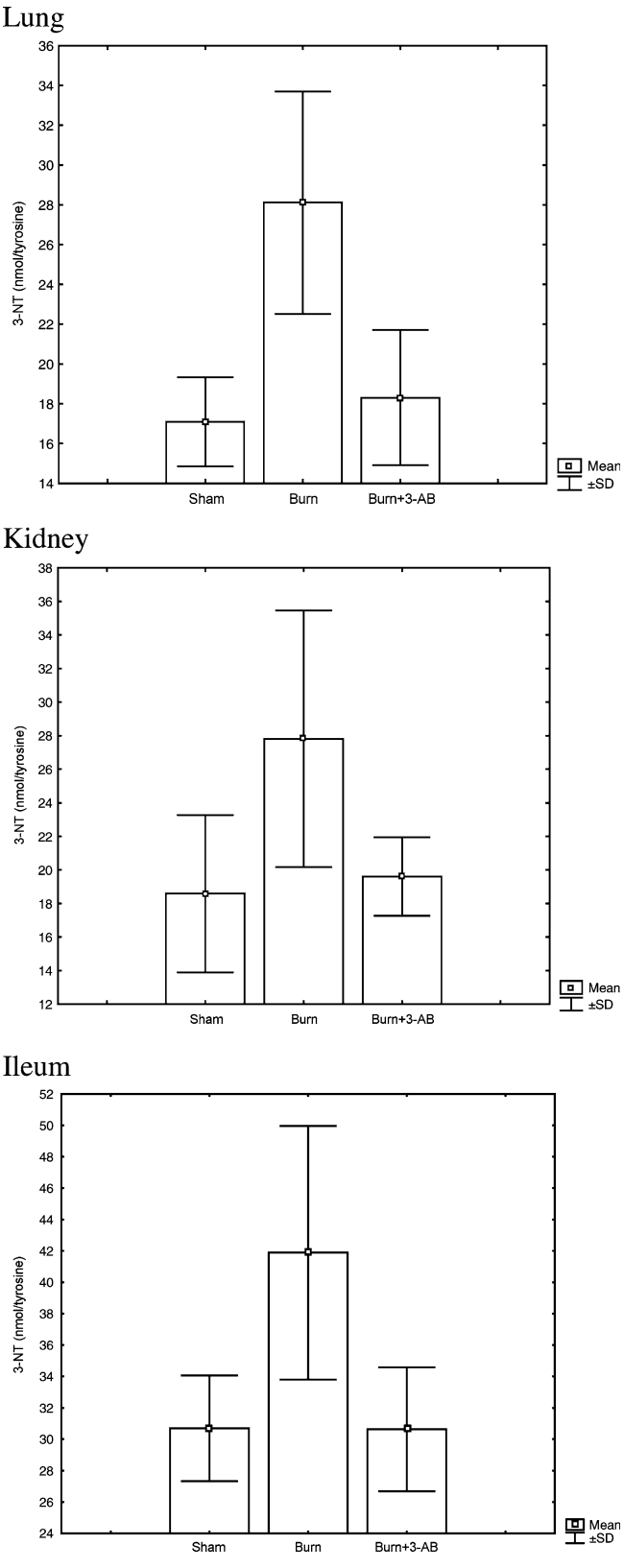

Fig. 3 3-NT levels in lung, kidney, and ileum in the burn group were significantly increased compared with the other groups ($p < 0.05$). Data are expressed as mean ± SD

peroxidation to reaction of $ONOO^-$ with lipids in the cellular membranes. Pretreatment 3-AB reduced the level of MDA in lung, intestine, and kidney. This set of data showed that lipid peroxidation was prevented by the PARS inhibition.

Thermal cutaneous injury leads to a transient splanchnic vasoconstriction, which causes intestine and kidney damage due to ischemia-reperfusion (I/R) injury [23, 24]. Reperfusion is typically associated with neutrophil accumulation, both local and systemic. Another important mechanism for distant organ damage after burn injury is neutrophil accumulation in systemic organs. Neutrophils are a potential source of ROS and RNS and have a major role in the development of oxidative and nitrosative tissue injury. Several studies have demonstrated that neutrophil accumulation in liver, lung, kidney, and gastric mucosa may be involved in the pathogenesis of burn injury in these distant organs [25, 24]. Recent work has suggested that $ONOO^-$ has a crucial role in neutrophil infiltration and tissue injury in I/R models. In the same studies, it has been revealed that PARS inhibition by 3-AB reduces neutrophil infiltration and prevents tissue injury [26, 27]. Additionally, Chen and coworkers showed that inhibition of iNOS not only reduces intestinal mucosal peroxynitrite levels and improves the barrier function of the intestinal mucosa [28], but it also prevents lung neutrophil deposition and damage in burned rats [29]. In parallel, in the present study, while MPO activity (which is known as the index of neutrophil infiltration in tissues) significantly increased in lung, intestine, and kidney in the burn group, PARS inhibition prevented the infiltration of neutrophils in these organs, as evidenced by reduced MPO activity in the burn-plus-3-AB group.

On the other hand, another possible mechanism is the alteration of interactions between leukocytes and endothelial cells, which are mediated by different adhesion molecules. P-selectin is a member of the selectin family and mediates rolling of leukocytes along the endothelium. Intercellular adhesion molecule-1 (ICAM-1), which is one of the most important ligands for leukocytes, mediates binding of leukocytes on the endothelium during the reperfusion [30]. These proinflammatory molecules are normally expressed at the basal level, but their expression can be enhanced by several cytokines in various inflammatory processes including IR injury and burn trauma [31, 32]. In several studies, beneficial effects of PARS inhibition have been documented in various tissue injury due to inflammation. Zingarelli et al. [33] demonstrated that PARS inhibition reduced the expression of P-selectin and ICAM-1 in an I/R model. In our study, although we did not study these adhesion molecules, PARS inhibition might also have reduced the expression of P-selectin and upregulation of ICAM-1 in tissues. Additionally, nuclear factor-kappa B (NF-κB), as a transcriptional regulatory protein, plays a central role in regulating cytokines and other mediators are involved in tissue injury associated with I/R [34]. Recently, Matata and Galinanes have demonstrated that

$ONOO^-$ enhances NF-kB-mediated proinflammatory signal transduction pathways [35]. Furthermore, it was reported that PARS activates the NF-κB pathway [36]. PARS inhibition presenting antiinflammatory and antioxidant effects may have a role in diminishing the activity of NF-κB in this experimental study.

Overall, peroxynitrite can cause DNA strand breakage, which triggers the activation of PARS. PARS plays an important role in repairing DNA strand breaks, and its activation results in a reduced cellular content in NAD^+ and ATP and ultimately leads to cell death [7, 12]. Thus, this process has been termed the "PARS suicide hypothesis" [13]. Many experimental studies have demonstrated that PARS inhibition has beneficial effects against organ dysfunction due to reperfusion injury and endotoxemia [13, 27, 37]. Shimoda et al. [38] have clearly demonstrated that PARS inhibition reduces both the morphological and the physiological changes in the lung in models of burn and smoke inhalation. The nitration of protein tyrosine residues by $ONOO^-$ results in the formation of 3-NT, the footprint of $ONOO^-$, and the appearance of this product in tissue samples is taken as a diagnostic tool for exposure to peroxynitrite [39]. However, 3-NT is unnecessary for the formation of $ONOO^-$ because other nitrating agents, such as myeloperoxidase, lactoperoxidase, and lipogenase, may also contribute to 3-NT formation [40]. Chen et al. [29] have reported that increased levels of 3-NT have been detected in rat intestinal mucosa following thermal injury [29]. In our study, we observed that the levels of 3-NT in lung, intestine, and kidney tissues were increased in the burn group and that they were decreased by pretreatment 3-AB in the burn-plus-3-AB group. Actually, administration of 3-AB did not completely prevent 3-NT formation in the burn-plus-3-AB group (Fig. 3). The partial decrease in the 3-NT level in the burn-plus-3-AB group was an indirect finding of the presence of a possible nitrating mechanism other than the $ONOO^-$ pathway. The rest of the 3-NT formation must be due to the contribution of other reactions, as mentioned before [20, 41]. We did not exclude other nitrating mechanisms leading to the formation of 3-NT, but we based this study on the idea that $ONOO^-$ is the most likely source in vivo.

In conclusion, thermal injury induces oxidative and nitrosative organ damage in different systems, and PARS inhibition reduces tissue injury in lung, intestine, and kidney after a burn. Damage to these organs in burn injury may be due to excessive $ONOO^-$ production. The results of this study suggest that the peroxynitrite-PARS pathway plays an important role in burn-induced systemic organ damage.

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