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Sodium butyrate inhibits the production of HMGB1 and attenuates severe burn plus delayed resuscitation-induced intestine injury via the p38 signaling pathway

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ABSTRACT

Background: Inflammatory response triggered by high mobility group box-1 (HMGB1) protein and oxidative stress play critical roles in the intestinal injury after severe burn. Sodium butyrate, a histone deacetylase inhibitor, has potential anti-inflammatory properties, inhibiting the expression of inflammatory mediators such as HMGB1 in diverse diseases. This study was designed to investigate the effects of sodium butyrate on severe burn plus delayed resuscitation-induced intestine injury, intestinal expressions of HMGB1 and intracellular adhesion molecule-1 (ICAM-1), oxidative stress, and signal transduction pathway changes in rats.

Materials and methods: Fifty-six Sprague-Dawley rats were divided into 3 groups randomly: (1) sham group, animals underwent sham burn; (2) burn group, rats subjected to full-thickness burns of 30% total body surface area (TBSA) and received 2 ml/kg/TBSA lactated Ringer solution for resuscitation at 6, 12, and 36 h after burn injury; (3) burn plus sodium butyrate (burn+SB) group, animals received burn injury and lactated Ringer solution with sodium butyrate inside for resuscitation in the same manner. Diamine oxidase (DAO) concentration in plasma was measured by enzyme-linked immunosorbent assay. Intestinal fatty acid binding protein (I-FABP) and ICAM-1 expressions in the intestine were analyzed by immunohistochemical method. HMGB1 and p38 mitogen-activated protein kinase (MAPK) expressions in the intestine tissues were examined by Western blot. The intestinal concentration of malondialdehyde (MDA) was also determined.

Results: Intestinal HMGB1 expression was significantly increased in burn group compared with sham group. Sodium butyrate administration significantly inhibited the HMGB1 expression in the intestine, decreased the DAO concentration in plasma, reduced the intestinal I-FABP expression, and improved the intestinal histologic changes induced by burn injury plus delayed resuscitation. Sodium butyrate treatment also markedly reduced the increase of intestinal ICAM-1 expression and MDA content, and inhibited p38 MAPK activity in the intestine of severely burned rats with delayed resuscitation.

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Conclusions: Sodium butyrate inhibits HMGB1 expression which could be attributed to p38 MAPK signal transduction pathway and decreases intestinal inflammatory responses and oxidative stress, thus attenuates burn plus delayed resuscitation-induced intestine injury.

1. Introduction

Prompt and adequate resuscitation has been documented to play a vital role in the outcome of severely burned patients [1]. However, in the rural areas, especially in the developing countries, the fluid resuscitation is frequently delayed due to the referral transportation and lack of burn knowledge. Inadequate or delayed fluid resuscitation leads to tissue hypoperfusion, which can result in early organ injury and failure [2]. Rapid infusion to replace loss of fluid within 2 h is effective to maintain vital organ function and prevent progressive organ damage [3]. The intestine is known to be exceedingly vulnerable to tissue hypoperfusion and hypoxia [4]. Delayed resuscitation after severe burns causes the intestinal tissue hypoxia-ischemia injury which presents with cell function disorder, injury, apoptosis, and even death. Besides the damage itself, the most significant harm of intestinal injury is that it can cause severe destruction of remote organs [5]. Damage of intestinal mucosa and barrier led to the bacteria and toxin translocation into liver and blood, which resulted in the development of systemic inflammatory response syndrome (SIRS) and secondary multiple organ dysfunction syndrome (MODS) [6–8]. MODS and sepsis are the two leading causes of death in major burn patients during the last two decades [9]. How to prevent and reduce the intestinal injury after major burns especially the patients with delayed resuscitation is a big challenge for the worldwide burn surgeons.

High mobility group box-1 (HMGB1) protein, a non-histone architectural chromosomal protein, is recognized as a monocyte-derived late-acting inflammatory mediator and is responsible for the production and release of several proinflammatory cytokines, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, intracellular adhesion molecule-1 (ICAM-1), in many inflammatory and infectious disorders [10,11]. More recent papers have shown that HMGB1 was involved in the development of intestinal ischemia-reperfusion injury and anti-HMGB1 antibody treatment improved the 48-h survival rate [12–14]. These results suggest that HMGB1 is an important trigger of the inflammatory response in intestinal injury.

Sodium butyrate is a short-chain volatile fatty acid, which is an important energy source for intestinal epithelial cells. Additionally, sodium butyrate is a histone deacetylase inhibitor and has potential anti-inflammatory properties, inhibiting the expression of inflammatory mediators such as HMGB1, nuclear factor-kappa B (NF-κB), affecting the intestinal barrier, and playing an important role in oxidative stress [15,16]. Our previous study demonstrated that sodium butyrate reduced the pulmonary HMGB1 expression, inhibited oxidative stress in the lungs, and alleviated burn-induced acute lung injury [17]. These findings suggest that sodium butyrate may protect against severe burn-induced intestine injury. Therefore, the present study was designed to determine the effects of sodium butyrate on severe burn-induced intestine injury, intestinal expression of ICAM-1, oxidative stress, and signal transduction pathway changes in severely burned rats with delayed resuscitation.

2. Materials and methods

2.1. Animals

Female healthy Sprague-Dawley rats weighing 200–250 g were housed in a controlled room and provided with standard animal chow and water; food and water were accessible at will during the course of the study procedure. At the end of study, the rats were sacrificed under general anesthesia with 30 mg/kg pentobarbital intraperitoneally. None of these rats died spontaneously.

This study was performed in accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The protocol was approved by the Anhui Medical University Ethics Committee of Animal Experiments in Hefei city, China (Permit Number: 20131071).

2.2. Experimental design, burn procedure and delayed resuscitation

Rats were randomized into the following 3 groups:

(1) Sham group (8 rats): normal animals were only immersed in room-temperature water and did not receive any fluid resuscitation.
(2) Burn group (24 rats): A 30% TBSA third-degree burn was obtained as described previously [18]. In brief, the rats were anesthetized with 30 mg/kg pentobarbital intraperitoneally. Then, the dorsal area was then de-haired and was immersed in 98 °C water for 12 s through a template device on the dorsal surface. At 6, 12, and 36 h after burn trauma, the animals were resuscitated with 2 ml/kg/TBSA lactated Ringer's solution intraperitoneally.
(3) Burn plus sodium butyrate (burn+SB) group (24 rats): The animals received a scald injury same to burn group. Sodium butyrate was diluted 1:150 in lactated Ringer's solution. The animals were resuscitated with sodium butyrate lactated Ringer's solution in the same manner at 6, 12, and 36 h after scald. That is, the dose of sodium butyrate given at each time point was 400 mg/kg.

Subsequently, the rats of burn group and burn+SB group were sacrificed at 12, 24, and 48 h after scald to sample their blood and intestinal tissue. The experiment design was shown in Fig. 1 of Supplementary materials.

2.3. Histologic examination of the intestine

A 3cm proximal ileum section was harvested at a distance of 10cm distal to the ligament of Treitz after sacrifice. The specimen was imbedded in 10% formalin, then was fixed in paraffin, and stained with hematoxylin and eosin. Histologic evaluations were categorized by two individual pathologists who were unaware of the study design and intestinal damage was scored using Chiu's method [19].

2.4. Measurement of diamine oxidase (DAO) concentration in plasma

Plasma concentration of DAO was measured by ELISA in accordance with the instructions provided by the manufacturer. The DAO ELISA kit for rat was from Nanjing Jiancheng Bioengineering Institute, Nanjing, China (Product No.: 50R-E.1783).

2.5. Immunohistochemical examination for intestinal fatty acid binding protein (I-FABP) and ICAM-1 expressions

Immunohistochemical stainings were performed on paraffin-embedded specimens with goat anti-I-FABP (Santa Cruz Biotechnology), or monoclonal antibody specific for ICAM-1(Santa Cruz Biotechnology). The immunoreaction was processed using UltraSensitive S-P Kit (Fuzhou Maixin Biotechnology Co., China) according to the instructions by the manufacturer. 3,3′-Diaminobenzidine was used as a chromogen. Brownish-yellow stained regions were recognized as areas with positive antigen expression.

2.6. Measurement of intestine malondialdehyde (MDA) concentration

The intestinal MDA concentration, an indicator of oxidative stress and lipid peroxidation [20], was examined by the thiobarbituric acid colorimetric method using a commercial kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) in accordance with the manufacturer's instructions. Briefly, frozen intestine tissues were weighed and homogenized (1:10, w/v) in normal saline in an ice bath. The homogenates were centrifuged at 900×*g* for 10min at 4°C. The MDA concentrations in the supernates were measured strictly following the recommendations of the manufacturer. Absorbance at 532nm was measured using a spectrophotometer and the MDA concentration was expressed as nmol/(mg protein).

2.7. Western blot analysis of intestinal HMGB1 and p38 mitogen-activated protein kinase (MAPK) expressions

Total protein extract was prepared and the concentration of protein was measured by bicinchoninic acid protein method. SDS-PAGE was utilized to separate the protein extracts. Then, they were electrotransferred to a nitrocellulose membrane. After the blocking process, the membranes were incubated with the primary antibodies overnight for HMGB1 (Cell Signaling Technology), phosphor-p38 (Santa Cruz Biotechnology), and p38 (Santa Cruz Biotechnology) followed by horseradish peroxidase-conjugated secondary antibodies. To detect immunoreactive bands, electrochemiluminescence Western blot detection system (Amersham, UK) was used.

2.8. Statistical analysis

All data were expressed as mean±SEM. We used ANOVA to interpret the results and LSD test was utilized to determine the between-group variance. We considered $p<0.05$ to be statistical significance.

3. Results

3.1. Sodium butyrate administration inhibits intestinal HMGB1 expressions of severely burned rats

The HMGB1 expression was expressed as relative densitometry of HMGB1/β-actin and the values were expressed as fold change from the sham rats in each comparison. After a 30% TBSA third degree burn trauma, HMGB1 expression was obviously increased in burn group compared with sham group, which was markedly decreased by sodium butyrate administration (Fig. 1A). Densitometric scan results showed that the intestinal HMGB1/β-actin ratios of burn group at 12, 24, and 48h post burn were 1.45, 1.62, and 2.01, respectively. Moreover, the intestinal HMGB1 protein expression levels in burn+SB group at 12, 24 and 48h after injury were 1.17, 1.23, and 1.11, significantly, which were significantly lower than those in related burn group (Fig. 1B).

3.2. Sodium butyrate decreases the plasma DAO concentration induced by severe burn injury

DAO is a functional intestinal marker enzyme. The concentration of DAO in plasma was determined by ELISA. At 24h after a 30% TBSA third degree burn, the plasma DAO level in burn group was distinctly higher than that in sham group ($p<0.05$). This concentration was significantly reduced in the burned animals that received sodium butyrate in comparison to burn group (Fig. 2). There was no significant difference in plasma DAO level between sham group and burn+SB group at 24h postburn.

3.3. Sodium butyrate decreases histopathologic changes induced by severe burn trauma

As shown in Fig. 3A, no destructive changes were found in the HE-stained intestine tissues from sham group. At 24h after a 30% TBSA third degree burn plus delayed resuscitation, the intestines of rats show histologic alterations characterized by intestinal edema, the loss of villi integrity and derangement, and inflammatory cells infiltration (Fig. 3B). These histopathologic changes were all improved by the administration with sodium butyrate (Fig. 3C). The Chiu's double-blind score system results showed that the intestinal histologic scores of rats increased significantly after severe burn injury (Fig. 3D). These increases were significantly inhibited by sodium butyrate treatment. The Chiu's score at 24h post burn was 1.88±0.13, which was significantly reduced by sodium butyrate administration (1.25±0.17; $p<0.001$).

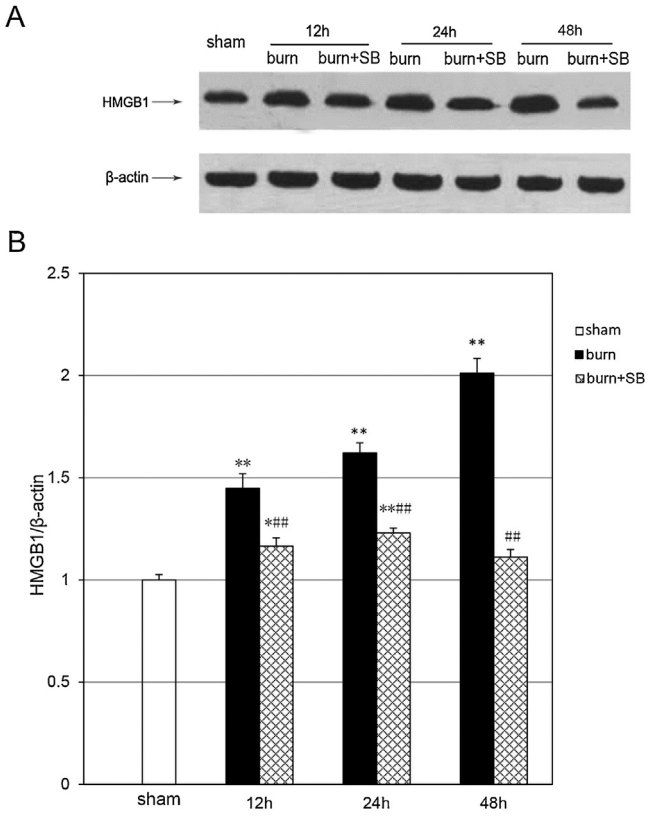

Fig. 1 – Effect of sodium butyrate on intestinal HMGB1 expressions. HMGB1 expression in the intestines was obviously increased in burn group in comparison with sham group. Administration with sodium butyrate resulted in a significant decrease in intestinal HMGB1 expression. (A) A representative result. (B) Results from the independent experiments given as mean ± SEM (n = 8). The HMGB1 expression was expressed as relative densitometry of HMGB1/β-actin. $^{*}p < 0.05$, $^{**}p < 0.01$, vs. sham group, ANOVA; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, vs. related burn group, ANOVA.

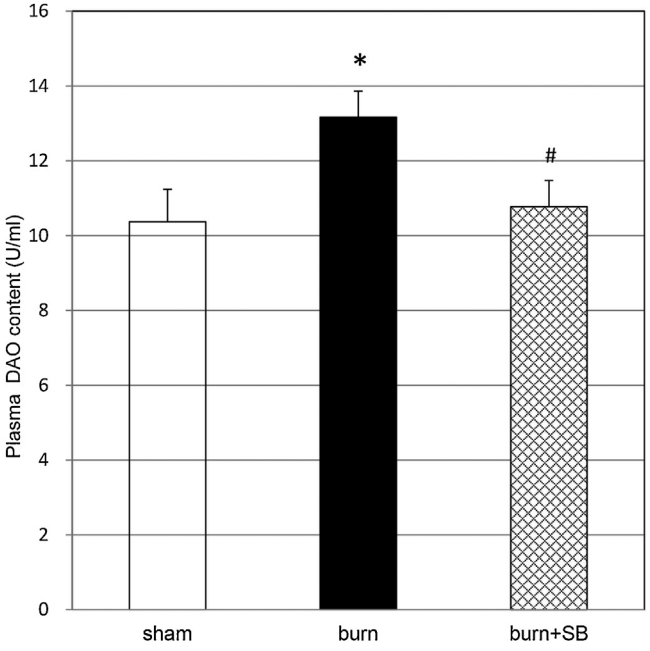

Fig. 2 – Effect of sodium butyrate on the plasma DAO concentration after burn injury. Severe burn injury and delayed resuscitation resulted in a significant increase in plasma DAO concentration whereas the values in animals receiving sodium butyrate were significantly lower and similar to sham group. Results were given as mean ± SEM (n = 8). $^{*}p < 0.05$, vs. sham group, ANOVA; $^{\#}p < 0.05$, vs. burn group, ANOVA.

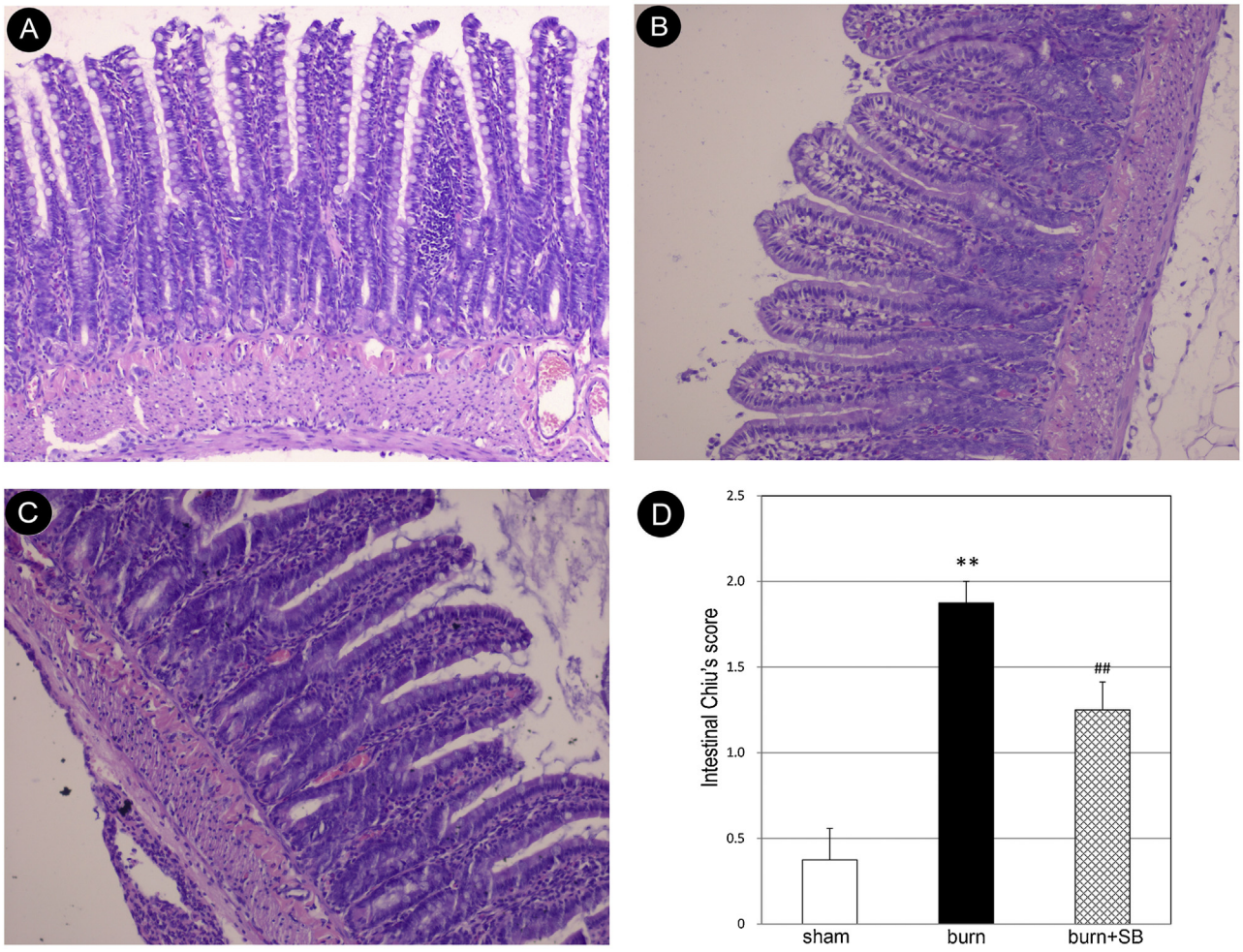

Fig. 3 – Effect of sodium butyrate on burn-induced histopathologic changes in rats (×100). Distal small intestines were harvested from animals 24 h following a 30% TBSA burn. (A) Section of normal small intestine from the sham rat. (B) Intestine of burn group animals displayed evidence of histological pathology characterized by intestinal edema, the loss of villi integrity and derangement, and inflammatory cells infiltration. (C) Gut sections harvested from rats of burn + SB group. (D) Intestinal Chiu's score by two pathologists blinded to the experimental conditions. Treatment with sodium butyrate attenuates intestinal injury induced by a 30% TBSA third degree burn and 6 h delayed resuscitation. Results were given as mean ± SEM (n = 8). $^{**}p < 0.01$, vs. sham group, ANOVA; $^{\#\#}p < 0.0$, vs. burn group, ANOVA.

3.4. *Sodium butyrate reduces the I-FABP and ICAM-1 expressions induced by severe burn injury*

I-FABP is a biochemical marker for early detection of intestinal epithelial injury. The intestinal expressions of I-FABP and ICAM-1 were detected immunohistochemically. I-FABP and ICAM-1 expressions were increased at 24 h after injury compared with sham group, both of which were markedly reduced to similar levels as sham group by sodium butyrate administration (Fig. 4).

3.5. *Sodium butyrate attenuates the intestine oxidative stress induced by severe burn trauma*

The intestine oxidative stress was assessed by intestinal MDA concentration. At 24 h after a 30% TBSA third degree burn, the intestinal MDA concentration increased significantly in burn group in comparison with sham group ($p < 0.05$). This concentration was markedly reduced by sodium butyrate administration. The intestinal MDA concentration in burn + SB group at 24 h after burn injury was significantly lower than that in burn group (Fig. 5).

3.6. *Sodium butyrate inhibits burn-induced p38 MAPK activation in intestinal tissues*

The phosphorylations of p38 MAPK were determined by Western blot analysis. As a result, p38 phosphorylation was significantly increased in intestinal tissue at 24 h after burn injury compared to sham burn controls (Fig. 6). Sodium butyrate administration significantly reduced p38 phosphorylation in the intestine and reductions up to 52.5% ($p < 0.01$). The mean density ratio of p-p38/p38 in the three (sham: burn: burn + SB) group was 1:2.17:1.03. No significant difference was found in total p38 expression between the groups.

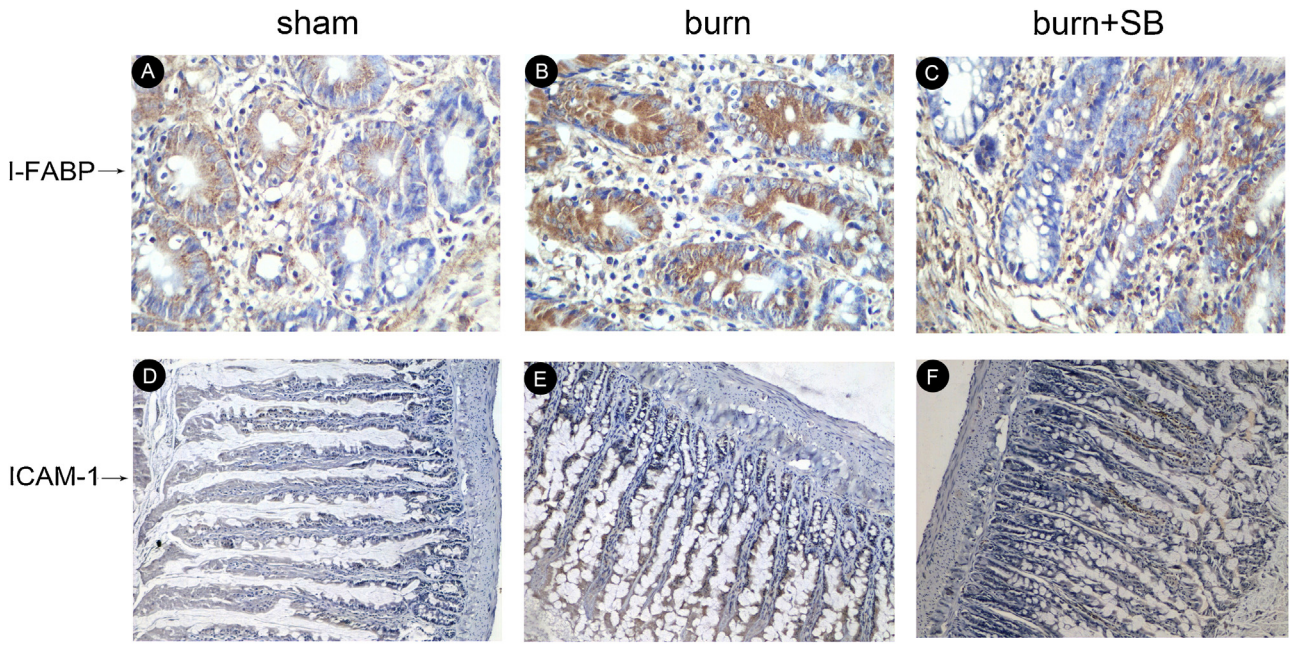

Fig. 4 – Effect of sodium butyrate on I-FABP and ICAM-1 expressions in intestine tissues. The I-FABP and ICAM-1 expressions in intestine increased significantly in the burned rats compared with the sham controls. Sodium butyrate administration decreased intestinal I-FABP and ICAM-1 expressions obviously. (A) Intestinal I-FABP expression of sham group. (B) Intestinal I-FABP expression of burn group. (B) Intestinal I-FABP expression of burn+SB group. (D) Intestinal ICAM-1 expression of sham group. (E) Intestinal ICAM-1 expression of burn group. (F) Intestinal ICAM-1 expression of burn+SB group.

4. Discussion

The most critical aspect of the early care of the burn patient is to restore and maintain adequate tissue perfusion and vital organ function. Intravenous resuscitation of burn patients has greatly improved outcomes and become a cornerstone of modern burn care. Establishment of intravenous lines for fluid resuscitation is necessary for all patients with major burns. However, the intravenous line is very difficult to stablish in

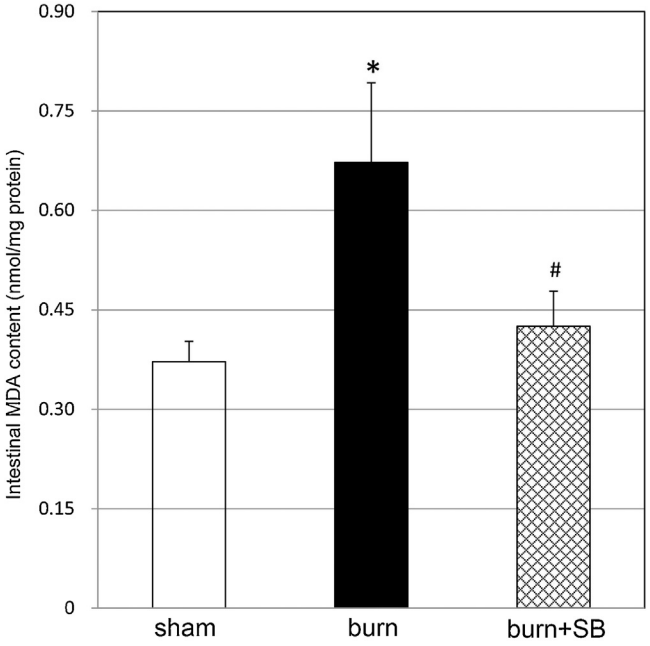

Fig. 5 – Effect of sodium butyrate on the intestinal MDA concentration. Intestinal MDA concentration increased significantly at 24h after burn injury, which was obviously attenuated by sodium butyrate treatment. Results were given as mean ±SEM (n=8). $^{*}p<0.05$, vs. sham group, ANOVA; $^{\#}p<0.05$, vs. burn group, ANOVA.

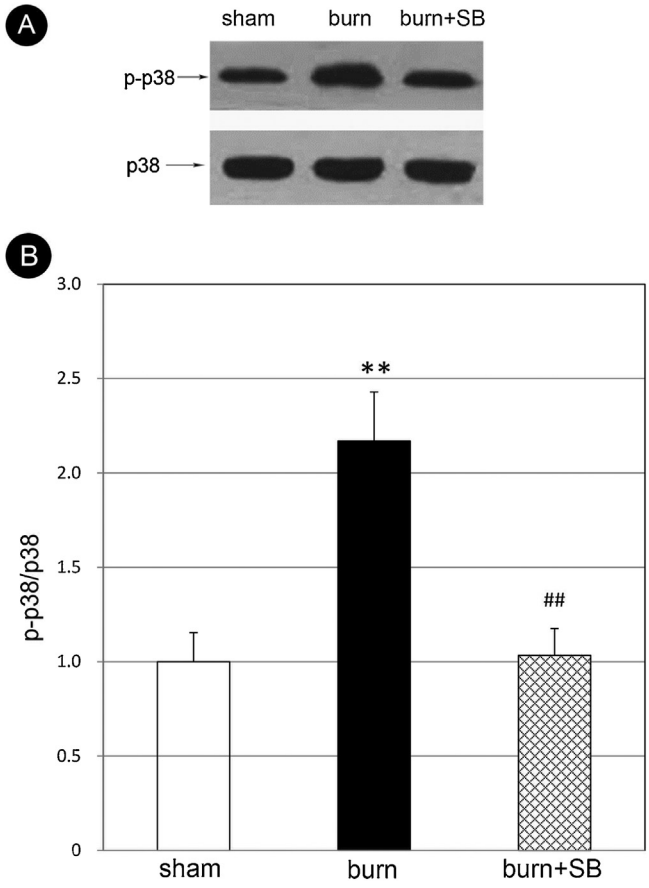

Fig. 6 – Effect of sodium butyrate on p38 MAP kinase activity in intestine tissues. Intestinal p38 MAP kinase activity increased significantly at 24 h after burn trauma, which was significantly attenuated by sodium butyrate treatment. (A) A representative result. (B) Results from the independent experiments. The p38 activity was expressed as relative densitometry of p-p38 to p38. Results were given as mean ± SEM (n = 8). $^{**}p < 0.01$, vs. sham group, ANOVA; $^{\#\#}p < 0.01$, vs. burn + SB group, ANOVA.

rats. In the most of experimental study on burn resuscitation, the animals were always resuscitated intraperitoneally. But this mean of resuscitation is not clinically viable in burned patients. Recently, enteral resuscitation with oral rehydration solution has been suggested to be a substitute of intravenous fluid therapy, particularly in austere environments, mass casualty, or delayed transport scenarios [21]. Gain insight into the new means of burn resuscitation could yield new research.

Without adequate resuscitation, tissue perfusion suffers and shock cascade is perpetuated in a severely burned patient. A selective reduction in blood flow to small intestine has been demonstrated during massive burns. Furthermore, the intestinal tract is one of the organs particularly susceptible to ischemia and early gut hypoperfusion is responsible for progressive gut dysfunction [22,23]. There is increasing recognition that gut is the motor of MODS in critical illness [22]. This study showed that a 30% TBSA third degree burn and 6 h delayed resuscitation causes intestinal morphological changes, such as intestine edema, the loss of villi integrity and derangement, and inflammation.

DAO is an intracellular enzyme weight of 250 kDa and exists in a high level of activity in the intestinal villi [24]. Intracellular DAO will get into peripheral blood in a stable state upon intestine mucosal damage and DAO may serve as a plasma marker of the injury and integrity of intestine mucosal [25]. I-FABP is a soluble protein with a low molecular weight of 15 kDa and acts on the uptake and intracellular transport of long-chain fatty acids [26–28]. It is specifically located in the cytoplasm of epithelial cells of small intestine and is newly used as a biomarker for intestinal epithelial cell damage during the early stages of diverse diseases [29,30]. In the present study, plasma DAO level and intestinal I-FABP expression were utilized as quantitative methods to evaluate the intestinal epithelial damage. As a result, plasma DAO level and intestinal I-FABP expression were both markedly increased in rats at 24 h after a severe burn trauma plus delayed resuscitation. Our result that the intestinal I-FABP expression was significantly higher in the burn group in comparison with the control group is consistent with the study of Mitidiero et al., who found that ileum I-FABP expression was markedly increased in the necrotizing enterocolitis [30]. These results confirmed the existence of intestinal injury following burn injury.

Sodium butyrate is the main end-product of intestinal microbial fermentation and has been previously

demonstrated to inhibit inflammatory reaction in diverse diseases [16,17,31]. In this study, we found that sodium butyrate treatment post burn decreased the plasma DAO level, inhibited the intestinal I-FABP expression, reduced the intestinal histologic scores, and improved the pathologic changes. The data from this study suggest that sodium butyrate protects against severe burn injury plus delayed resuscitation-induced intestine injury.

HMGB1, a nuclear factor, is extracellularly released following extensive burn injury [32,33]. Plasma HMGB1 concentrations were found to be correlated with the complication of systemic infection and fatal outcomes in severely burned patients [32,33]. Our previous study also demonstrated that HMGB1 triggered inflammatory response in the lung after burn trauma [17]. Recently, HMGB1 has been implicated in intestinal injury [12–14]. In the current study, the intestinal HMGB1expression was significantly increased concomitant with the increase of intestine injury following burn trauma. Administration with sodium butyrate significantly decreased the production of HMGB1 and attenuated severe burn-induced intestinal injury.

It was recently shown that HMGB1 was able to stimulate the release of ICAM-1 which mediated the endothelium-neutrophil interactions and played an important role in organ injury [16,34]. Therefore, we further determined burn-induced ICAM-1 expressions in the intestine. As a result, intestinal ICAM-1 expression was evidently elevated after thermal injury and this increase was decreased by sodium butyrate treatment. These results showed that sodium butyrate administration attenuated the cascade releases of inflammatory mediators induced by severe burn injury, which may be a crucial mechanism for the protective effects of sodium butyrate on severe burn plus delayed resuscitation-induced intestine injury in rats.

Besides proinflammatory cascade, oxidative stress and lipid peroxidation have been shown to be a major causative agent of contributing to the gut epithelial cell damage [35,36]. MDA is the last product of lipid breakdown [37]. In this study, the cellular injury resulted from the release of reactive oxygen species because of oxidative stress and lipid peroxidation was assessed by the MDA concentrations in intestine homogenates of rats. Our results showed that the intestinal MDA level evidently increased after severe burn plus delayed resuscitation, which was significantly reduced by sodium butyrate treatment. These data suggest that sodium butyrate administration attenuates oxidative stress in the intestine after burn injury and delayed resuscitation.

p38 MAPK is one of the main signal pathways that regulate the production of inflammatory cytokines and oxidative stress in diverse diseases [38,39]. Stimulation of p38 MAPK leads to the initiation and activation of oxidative stress and a multitude of proteins essential to the inflammatory process [39,40]. It has been recorded in detail in our previous studies that inhibition of p38 MAPK reduced the proinflammatory response and release of reactive oxygen species following thermal injury, thus attenuating burn-induced liver and lung injury [18,41–43]. So far, the effect of sodium butyrate on p38 MAPK activation remains controversial. Qiu et al. [44] demonstrated that 5 and 10mM sodium butyrate both increased the p38 phosphorylated form in porcine intestinal epithelial cells. In the current study, we found that expression of phosphorylated p38 MAPK was significantly increased in the intestine tissue after burn injury and sodium butyrate administration inhibited the p38 activation concomitant with the decrease of HMGB1 and ICAM-1 and oxidative injury. This is consistent with the study of Khan et al., who found that pre- and post-treatment with sodium butyrate both significantly decreased the diabetes-induced p38overexpression in the islets of juvenile rat [45]. The discrepancy of sodium butyrate on p38 MAPK activation may vary according to the animal model, cell and organ type, administration time, dosage and route, and so on. The data from the present study suggest that sodium butyrate inhibits the production of HMGB1 following severe burn injuries by the means of the p38 MAPK signal transduction pathway, and is responsible for the protection from burns plus delayed resuscitation-induced intestinal injury. The potential p38 upstream activators of sodium butyrate in the intestine after severe burn injury remain to be addressed in further studies.

In summary, the data of this study suggest that sodium butyrate decreases intestinal inflammatory responses and oxidative stress, which correlates with inhibiting HMGB1 expression through p38 MAPK signal transduction pathway, and attenuates burns plus delayed resuscitation-induced intestinal injury. Our previous study showed that sodium butyrate protected against severe burn-induced lung injury [17]. Taken together, the data suggest that sodium butyrate exerts anti-inflammatory and anti-oxidative stress effects and may be a promising treatment to reduce burns plus delayed resuscitation-induced organ damage, which has to be proven in future clinical trials.

Conflict of interest

None.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.burns.2018.09.031.

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