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The Effect of Ethyl Pyruvate on Oxidative Stress in Intestine and Bacterial Translocation After Thermal Injury

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Background. **Thermal injury causes a breakdown in the intestinal mucosal barrier due to ischemia reperfusion injury, which can induce bacterial translocation (BT), sepsis, and multiple organ failure in burn patients. The aim of this study was to investigate the effect of ethyl pyruvate (EP) on intestinal oxidant damage and BT in burn injury.**

Materials and methods. **Thirty-two rats were randomly divided into four groups. The sham group was exposed to 21°C water and injected intraperitoneal with saline (1 mL/100 g). The sham + EP group received EP (40 mg/kg) intraperitoneally 6 h after the sham procedure. The burn group was exposed to thermal injury and given intraperitoneal saline injection (1 mL/100 g). The burn + EP group received EP (40 mg/kg) intraperitoneally 6 h after thermal injury. Twenty-four hours later, tissue samples were obtained from mesenteric lymph nodes, spleen, and liver for microbiological analysis and ileum samples were harvested for biochemical analysis.**

Results. **Thermal injury caused severe BT in burn group. EP supplementation decreased BT in mesenteric lymph nodes and spleen in the burn + EP group compared with the burn group ($P < 0.05$). Also, burn caused BT in liver, but this finding was not statistically significant among all groups. Thermal injury caused a statistically significant increase in malondialdehyde and myeloperoxidase levels, and EP prevented this effects in the burn + EP group compared with the burn group ($P < 0.05$).**

Conclusion. **Our data suggested that EP can inhibit the BT and myeloperoxidase and malondialdehyde production in intestine following thermal injury, suggesting anti-inflammatory and anti-oxidant properties of EP.**

Key Words: **intestinal mucosal barrier; thermal injury; ethyl pyruvate; bacterial translocation.**

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INTRODUCTION

Although the management of thermal injury has progressed in recent years, its complications such as systemic inflammatory response syndrome, sepsis, and multiple organ failure still continue to be the principal causes of mortality and morbidity [1]. Normally in the gut, there is homeostasis between the intraluminal bacteria, their products, and intestinal mucosal barrier [2]. Thermal cutaneous injury causes a breakdown in the intestinal mucosal barrier, which can induce bacterial translocation (BT), and thus septic complications and multiple organ failure in burn patients. After thermal injury, a transient and selective splanchnic vasoconstriction occurs which is related to decrease mesenteric blood flow and damage of the mucosal barrier due to ischemia reperfusion (I/R) injury, which promotes BT from the gut [3]. Pathophysiological mechanisms that lead to the injury of the mucosal barrier include the adhesion and activation of polymorphonuclear neutrophils, the release of pro-inflammatory cytokines, as well as the formation of reactive oxygen species (ROS), such as hydroxyl radical, superoxide anion, hydrogen peroxide, and reactive nitrogen species, such as nitric oxide and peroxynitrite [4]. ROS are thought to play a major role in the pathogenesis of structural and functional alterations in the tissues, which are related to a variety of pathologic processes, such as sepsis and septic shock [5, 6], hemorrhagic shock [7], and thermal injury [8].

Pyruvate, a small molecule that normally is regarded as a key intermediate in the oxidative or anaerobic metabolism of glucose, is also a potent and effective ROS scavenger [9, 10]. Pyruvate's antioxidant properties stem in part from its alpha-keto-carboxylate structure, which enables it to directly nonenzymatically neutralize peroxides and peroxynitrite [11]. It has

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been shown recently that pyruvate is also capable of scavenging hydroxyl radical [12]. After recognition of pyruvate as a ROS scavenger, multiple investigators tried using this compound for the treatment of various pathologic conditions [10], including organ injury and dysfunction in animal models of redox stress such as transient myocardial [13], intestinal [14], or hepatic [15] ischemia followed by reperfusion. However, the usefulness of pyruvate as a therapeutic agent has been limited by its poor solubility in solution [10]. Ethyl pyruvate (EP) is a derivative of pyruvic acid and cleaves in the body into ethanol and pyruvic acid.

To circumvent the poor solubility of pyruvate, EP has been formulated in a Ca^{2+}- and K^{+}-containing solution named Ringer's ethyl pyruvate solution (REPS) [16]. It has been shown that REPS is an effective anti-inflammatory agent and this solution can improve the outcome in a variety of animal models of critical illness, such as hemorrhagic shock, sepsis and ischemia, and reperfusion injury [10]. Prompted by these observations, we hypothesized that treatment with REPS might be beneficial to oxidative stress and bacterial translocation in intestine after thermal injury.

MATERIALS AND METHODS

The procedures used in this study and handling of the study animals were performed in adherence to National Institutes of Health guidelines on the use of experimental animals. The experimental protocol was approved by the Ethical Committee of Ankara Education and Research Hospital.

EP was purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany) and was used to prepare REPS containing 130 mM Na^{+}, 4 mM K^{+}, 2.7 mM Ca^{2+}, 130 mM Cl^{-1}, and 28 mM EP.

Animals

Thirty-two Wistar rats, weighing between 200 and 250 g, were used in this study. The rats were housed at a constant temperature with a 12-h light–dark exposure. Animals were allowed access to standard rat chow and water *ad libitum* for an acclimation period of at least 1 week before use in this study.

Thermal Injury

Animals were anesthetized by intramuscular injection of ketamine hydrochloride (50 mg/kg) and xylazine (5 mg/kg). The burn model described by Walker and Maso was used in this study [17]. The backs of the animals were shaved to allow direct skin contact between skin and hot water. A marked area of the shaved dorsal skin was exposed through a template and immersed in boiling water for 12 s. This procedure produced a full-thickness burn of 30-35% of total body surface area of the rats. The sham control animals were exposed to room temperature water in an identical setting. All animals in groups II and IV were resuscitated with 1 mL/100 g saline intraperitoneally following burn injury. After recovering from anesthesia, all animals were allowed access to water and standard rat chow. No animals died within the 24 h postburn period.

Experimental Design

After the stabilization period, the 32 rats were randomly divided into four groups. The first group (sham group, $n = 6$) was exposed to 21°C water and intraperitoneal saline injection (1 mL/100 g). The second group (sham + EP, $n = 8$) received EP (40 mg/kg) intraperitoneally after 6 h from the sham procedure. The third group (burn group, $n = 8$) was exposed to thermal injury and given an intraperitoneal saline injection (1 mL/100 g). The fourth group (burn + EP group, $n = 8$) received EP (40 mg/kg) intraperitoneally after 6 h from thermal injury. All animals were sacrificed 24 h after thermal injury. A midline laparotomy was performed and mesenteric lymph nodes (MLN), spleen, and liver specimens were obtained under sterile conditions. Then, samples of ileum were harvested for biochemical evaluation.

Microbiological Analysis

The blood samples of all animals were obtained through the vena cava, inoculated to blood culture medium including brain heart infusion (BHI), and incubated at 37°C for 7 days under aerobic conditions. The tissue specimens were extracted from liver, spleen, and MLN, respectively, to indicate the bacterial translocation. Then they were weighed and placed into a glass homogenizer under sterile conditions. After the liver and spleen were homogenized into 2 mL BHI, 0.1 mL of these samples was inoculated with blood agar and McConkey agar. MLN was homogenized into 5 mL BHI and then its serial solutions were prepared from this homogenate. A 0.1 mL sample of each solution was inoculated with blood agar and McConkey agar. All cultures were incubated under aerobic conditions at 37°C and were examined at 24 and 48 h for the presence of growth. The identification of bacterial species was performed by standard microbiological methods. Colonization was expressed as the number of colony-forming units per gram of tissue homogenate (CFU/g).

Measurement of Myeloperoxidase (MPO) Activity

Tissue-associated MPO activity in intestinal mucosa was determined using the method of Grisham *et al.* [18]. Samples of intestinal mucosa (300 mg) were homogenized in 5 mL ice-cold 0.02 M EDTA (pH 4.7) for 60 s. Five milliliters of mucosal homogenate was centrifuged at 20,000 × *g* for 15 min at +4°C to pellet the insoluble cellular debris. The supernatant, which contained less than 0.5% of total MPO activity, was discarded. The pellet was then rehomogenized in an equivalent volume of 0.05 M potassium phosphate buffer (pH 6.0) containing 0.5% hexadecyltrimethylammonium bromide. This homogenate was centrifuged at 20,000 × *g* for 15 min at +4°C and supernatants used MPO assay. MPO activity was assessed by measuring the H_2O_2-dependent oxidation of *o*-dianisidin. One unit of enzyme activity was defined as the amount of MPO present that caused a change in absorbance of 1.0/min at nanometers and 37°C [19].

Measurement of Malondialdehyde (MDA) Levels

The level of MDA was determined by intestinal mucosa homogenized by a ratio of 1/10 (w/v) in 1.15% cold KCl solution, by the aid of thiobarbituric acid method (TBA). The TBA method is the most widely used method for assessing lipid peroxidation. The principal of the method is based on the measurement of absorbance of the pink color produced by interaction of TBA with MDA at 530 nm [20]. Results were expressed as nmol/g tissue weight.

Statistical Analysis

Data are reported as the mean ± SEM, or mean ± SD when appropriate. Differences between means were evaluated by one-way analysis of variance. If the data were not normally distributed, the Mann–Whitney *t*-test (Wilcoxon rank sum test) was used to analyze treatment groups. Statistical significance was accepted as $P < 0.05$. The statistical analyses were performed by SPSS, version 13.0 for Windows (SPSS Inc., Chicago, IL).

TABLE 1

The Quantitative Results of Bacterial Translocation in Tissue Specimens

Groups	MLN (CFU/g)	Spleen (CFU/g)	Liver (CFU/g)
Sham ($n = 6$)	700.20 ± 1320.02	90.3 ± 90.3	471.58 ± 265.29
Sham + EP ($n = 8$)	740.58 ± 1422.09	44.74 ± 18.45	493.89 ± 368.44
Burn ($n = 8$)	12,753.53 ± 19,680.98*	2982.93 ± 759.04*	2563.21 ± 1420.00
Burn + EP ($n = 8$)	1380.61 ± 3244.18†	67.95 ± 47.64†	468.60 ± 132.98

Note. Values are expressed as mean (CFU/g tissue) ± SEM.
* $P < 0.05$ compared with other groups.
† $P < 0.05$ compared with the burn group.

RESULTS

All animals survived during the experimental period. The incidence of BT within the groups is summarized in Table 1.

Thermal injury caused severe BT in the burn group, and the quantity of bacteria isolated from MLN and spleen, was significantly higher in that group than the other groups ($P < 0.05$). EP supplementation prevented BT in MLN and spleen in the burn + EP group, and the decrease in BT was statistically significant compared with the burn group ($P < 0.05$). Also, burn caused BT in liver, but this finding was not statistically significant among all groups ($P > 0.05$). The predominating bacterium was *Escherichia coli*.

The results of the biochemical analysis in the tissue specimens are presented in Table 2. MDA levels were significantly increased in the burn group in comparison to the other groups ($P < 0.05$). MDA levels were significantly reduced in the burn + EP group compared with the burn group ($P < 0.05$). Similar to these findings, thermal injury caused a statistically significant increase in MPO levels in the burn group compared with the other groups ($P < 0.05$). MPO levels were significantly reduced in the burn + EP group compared with the burn group ($P < 0.05$).

DISCUSSION

The present study demonstrated that burn-induced BT was prevented by EP in MLN and spleen. Furthermore, the elevated lipid peroxidation and MPO activity were decreased by EP after thermal injury.

TABLE 2

The Results of Biochemical Analysis of Tissue Samples

Groups	MDA (nmol/g tissue)	MPO (U/g)
Sham ($n = 6$)	12.80000 ± 1.09909	0.31633 ± 0.048984
Sham + EP ($n = 8$)	9.4500 ± 1.08960	0.18710 ± 0.052427
Burn ($n = 8$)	18.4250 ± 0.85315*	0.52825 ± 0.051906*
Burn + EP ($n = 8$)	15.4250 ± 0.82419†	0.39675 ± 0.060575†

Note. Values are expressed as mean ± SD.
* $P < 0.05$ compared with the other groups.
† $P < 0.05$ compared with the burn group.

Ischemia and consecutive reperfusion cause oxidative stress, which is characterized by an imbalance between ROS and the anti-oxidative defense system [21]. In many studies it has been shown that burn injury is associated with lipid peroxidation, which is believed to be an important cause of oxidative damage to cellular membranes, and eventually, cell death [22]. Recently, Horton clearly revealed the role of ROS and reactive nitrogen species on lipid peroxidation in burn injury [23]. MDA is a good indicator of oxidative injury and an end product of lipid peroxidation. Several studies have demonstrated that burn injury and I/R injury are associated with elevated levels of MDA in different organs and tissues [22, 24, 25]. In this study, the levels of MDA and MPO significantly increased in intestinal tissue after thermal injury and EP decreased both MDA and MPO levels. This protective effect of EP largely depends on its anti-inflammatory and ROS scavenger effects.

In previous studies, EP has been shown to ameliorate intestinal, renal, or hepatic injury when it is used as a therapeutic agent to treat rodents subjected to mesenteric ischemia and reperfusion [16, 26], hemorrhagic shock [27], endotoxemia [28], or polymicrobial bacterial sepsis [28, 29]. Treatment with EP also ameliorates organ dysfunction in murine models of acute pancreatitis [30] and alcoholic hepatitis [31]. In these models of acute critical illness, treatment with EP down-regulates the expression of various pro-inflammatory genes, including nitric oxide synthase, tumor necrosis factors, cyclooxygenase-2, and interleukin-6—in liver, ileal mucosal, and colonic mucosa with EP [10].

EP has also been studied in rat models of burn injury [32–34]. Wang *et al*. showed that EP can obviously improve the outcome with delayed resuscitation and prevent the development of multiple organ dysfunction after burn injury [32].

It has been demonstrated that EP decreased activation of the pro-inflammatory transcription factor, nuclear factor (NF)-κB, in liver and colonic mucosa after

resuscitation from hemorrhagic shock in a murine model [27]. These findings suggested that EP may have activity as an anti-inflammatory agent. The I/R injury of the small intestine has been shown after thermal injury. Potential mechanisms leading the development and progression of I/R injury include the release of pro-inflammatory cytokines, as well as the formation of ROS [35].

A pharmacologic ROS scavenger must limit the oxidation of endogenous molecules and be present in the milieu where ROS are being generated. EP is chemically closely related to the endogenous metabolite pyruvic acid, a compound that is well known to be an effective scavenger of the ROS, hydrogen peroxide [36]. Therefore, in addition to its properties as an anti-inflammatory agent, it also has been shown that to inhibit lipid peroxidation induced by hemorrhagic shock *in vivo* or by exposure to LPS *in vitro* [37]. Reduction of lipid peroxidation also paralleled with the change in MPO activity, which is known as the index of infiltration of polymorphonuclear neutrophils. Polymorphonuclear neutrophils are a potential source of ROS and have a major role in the development of oxidative tissue injury. Experimental studies have shown that MPO activity increases in several inflammatory processes, such as I/R injury [27], burn injury [38], and cecal ligation and puncture–induced sepsis [39]. In a recent study, it has been demonstrated that MPO activity increases in lung, liver, and intestine at 24 h after burn injury [37]. In the present study, we have demonstrated that MDA and MPO levels were decreased by EP after thermal injury, suggesting anti-inflammatory and anti-oxidant properties of EP in thermal injury induced inflammation and ROS production. The anti-inflammatory effects of EP may be caused by some sort of persistent modification of the cellular milieu caused by the compound, possibly as a result of a covalent interaction with an intracellular target. One such target could be the reduced form of the cysteine-containing tripeptide, glutathione. It is known that pyruvate reacts reversibly with cysteine to form an unstable thiazolidine adduct [40]. Furthermore, depletion of glutathione by other means has been shown to inhibit DNA binding by the important pro-inflammatory transcription factor (NF-κB) [41].

In the literature, different doses of EP, ranging from 40 to 150 mg/kg, were administered in various animals models such as sepsis, ileus, and I/R [26, 28, 36]. In this study, we also administered 40 mg/kg.

In summary, our data support the finding that EP can inhibit the bacterial translocation and MPO and MDA production following thermal injury. Further study is necessary to lead to clinical trials for the prevention of the devastating effects of thermal injury in burn patients.

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