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Protective effect of trapidil against oxidative organ damage in burn injury

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Abstract

Animal models of thermal injury indicate reactive oxygen species and inflammatory cytokines as causative agents in tissue injury on various organs distant from the original wound. Trapidil has various properties, such as inhibition of platelet aggregation and lipid peroxidation as well as reduction of the inflammatory response to injury. This study was designed to determine the possible protective effect of trapidil treatment against oxidative organ damage in lung, intestine and kidney induced by cutaneous thermal injury.

Thirty Wistar rats were randomly divided into five groups. Sham group ($n = 6$) was exposed to 21 °C water while burn-3 h group ($n = 6$) and burn + trap-3 h group ($n = 6$), burn-24 h ($n = 6$) and burn + trap-24 h groups were exposed to boiling water for 12 s to produce a full thickness burn in 35–40% of total body surface area. In both burn + trap-3 h and burn–trap-24 h group, 8 mg/kg trapidil was given intravenously immediately after thermal injury. Three and 24 h later, tissue samples were taken for biochemical analysis from lung, intestine and kidney and blood samples were obtained to determinate serum TNF-α levels. Cutaneous thermal injury caused a significant increase in myeloperoxidase (MPO) activity and malondialdehyde (MDA) and 3-nitrotyrozine (3-NT) levels in all tissues and elevated serum TNF-α levels at post-burn 3 and 24 h. Trapidil treatment significantly reduced in biochemical parameters, as well as serum TNF-α levels. These data suggest that trapidil has a protective effect against oxidative organ damage in burn injury.
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Keywords: Burn injury; Trapidil; Nitric oxide; TNF-α; Lipid peroxidation; 3-Nitrotyrosine

1. Introduction

Despite recent advances in the management of burn care, thermal trauma may cause damage to multiple organs distant from the original burn wound and may lead to multiorgan failure. 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 mechanisms of tissue injury remains unclear, there is increasing evidence that both oxidative and nitrosative stress have an important role in the development of multiorgan failure after thermal injury [1,2].

After thermal trauma, all tissues are subjected to ischemia and consequently, especially during burn resuscitation, reperfusion injury occurs [3,4]. Recently, several studies suggested that oxidative and nitrosative stress initiate an inflammatory cascade that includes acute phase protein synthesis, upregulation of inflammatory adhesion molecules and pro-inflammatory cytokine, such as interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α), release in ischemia reperfusion injury and burn injury [3,5,6]. Activated inflammatory cascade causes local and systemic neutrophil sequestration, which is source of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Thus, tissue or organ injury after thermal trauma appears to be mediated by both ROS and RNS, such as hydroxyl radical, superoxide anion, hydrogen peroxide, nitric oxide (NO) and peroxyni-

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trite ($ONOO^-$) [7]. Several studies have demonstrated that infiltrated neutrophils lead to formation of ROS, thereby contributing to organ injury distant from the original burn wound [4,8]. It has been shown that burn injury, associated with lipid peroxidation, mediated by ROS, is believed to be an important cause of oxidative damage to cellular membranes, and eventually cell death [9]. Furthermore, NO has been implicated in the pathogenesis of inflammatory processes including burn injury [2], and it participates in the regulation of microcirculation in several systems in both physiologic and pathological settings [10].

Trapidil which is clinically used as an antianginal drug, is a phosphodiesterase and platelet-derived growth factor inhibitor [11]. The pharmacological properties of trapidil include nitroglycerine-like vasodilatation, inhibition of platelet aggregation via thromboxane A_2 (TxA_2) inhibition, facilitation of the biosynthesis of prostacyclin and reduction of lipid peroxidation [12,13]. Moreover, trapidil inhibits secretion of interleukin-6 (IL-6) and interleukin-12 (IL-12) and suppresses production of TNF-α [14].

Recently, it has been demonstrated that trapidil has protective effects of different experimental I/R and inflammatory models [15–17]. However, it appears that there is no published data about the effects of trapidil on different systems after thermal injury. For this reason, in this study, we aimed to investigate whether trapidil had any beneficial effects on burn-induced organ damage in rat. Furthermore, we have also investigated the relationship between trapidil and peroxynitrite pathway in present study.

2. Materials and methods

2.1. Animals

The experimental procedures performed in this study were in concordance with the guidelines of 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. Animals were allowed to access to standard rat chow and water ad libitum. A 1-week period of acclimatization was used in this study.

2.2. Experimental design

After stabilization period, 30 rats were randomly divided into five groups. The first group (sham group, $n = 6$) was exposed to 21 °C water and vehicle (saline, 1 ml/100 g) was administered intravenously (i.v.). The second group (burn-3 h group, $n = 6$) was exposed to thermal injury and was given vehicle i.v. immediately after burn. The third group (burn + trapidil-3 h group, $n = 6$) received thermal injury and 8 mg/kg trapidil (Rocornal UCB, Germany) was administered intravenously immediately after the burn. Group IV (burn-24 h group) was exposed to thermal injury and vehicle was administered i.v. immediately after burn. Fifth group (burn + trapidil-24 h group) was exposed to thermal injury and trapidil was administered i.v. immediately after burn. In groups IV and V, the injections of trapidil or vehicle were repeated at 12 h following burn injury. All animals in groups II and III were sacrificed 3 h after thermal injury whereas the animals in groups IV and V were sacrificed 24 h after burn injury. A midline laparotomy was performed and the samples of ileum, kidney and lung were harvested for biochemical evaluation. Then, the blood samples were obtained for serological and biochemical analysis by cardiac puncture.

2.3. Thermal injury

Animals were anaesthetized with intramuscular injections of ketamine hydrochloride (50 mg/kg) and morphine sulphate (15 mg/kg). The burn model described by Walker et al. was used in this study [18]. The backs of animals 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 total body surface of the rat. The rats in sham group were exposed in identical setting where room temperature water (21 °C) was used instead of boiling water. All animals in groups II, III, IV and V were resuscitated with intraperitoneally injection of 2 ml/100 g saline following burn injury and were allowed to feed ad libitum with water and standard rat chow after recovering from anaesthesia.

2.4. Detection of MDA levels

Tissues were homogenized in 0.15 mM KCI for malondialdehyde (MDA) determination. After the homogenate had been centrifuged at 3000 rpm, the MDA levels in tissue homogenate supernatant, and plasma were determined by thiobarbituric acid (TBA) reaction according to Hiroshi and Yagi. The principle of the method depends on the colorimetric measurement of the intensity of the pink colour produced by the interaction of the barbituric acid with MDA. The colour reaction with 1,1,3,3 tetraethoxypropane was used as the primary standard [19].

2.5. Measurement of tissue myeloperoxidase (MPO) activity

Myeloperoxidase (MPO) is a haem-containing enzyme within the azurophil granules of neutrophils; therefore. measurement of MPO activity was used as a simple quantitative method for detecting leukosequestration. A tissue specimen of 300 mg was homogenized in 0.02 M EDTA (pH 4.7) in a Teflon Potter homogenizer. Homogenates were centrifuged at 20,000 × g for 15 min at +40 °C. After pellet was re-homogenized in 1.5 ml 0.5%

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