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Reno-protective effects of TAK-242 on acute kidney injury in a rat model

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ABSTRACT

Acute kidney inschemia/reperfusion (I/R) injury is characterized by an abrupt loss of kidney function, resulting in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes. Despite the advances in therapeutic techniques, the mortality and morbidity of patients remain high and have not appreciably improved. This study aims to evaluate the potential protective effect of TAK-242 on renal ischemia/reperfusion injury using an animal model. Thirty-five adult male Sprague-dawely rats (weighing 200–300), were assigned randomly into the following experimental groups ($n = 7$ in each group), Control (I/R), Sham (negative control), TAK-242 (5 mg/kg body weight), TAK-242 (10 mg/kg body weight) and Vehicle (DMSO). Rats were exposed to a 30 min of ischemia then 3 h of reperfusion. At the end of reperfusion phase, rats were sacrificed then plasma, serum and tissue samples were obtained to measure markers of kidney oxidative stress and inflammation. Plasma levels of neutrophil gelatinase-associated lipocalin (NGAL), and tissue levels of interleukin-18 (IL-18) and malondialdehyde (MDA) were significantly lower in TAK-242 pretreated groups than the vehicle group and the control group ($p < 0.05$). Furthermore; serum levels of urea and creatinine were significantly lower in the TAK-242 pretreated groups as compared to the control group ($p < 0.05$). We conclude that administration of TAK-242 can be useful preventive method in attenuating the degree of acute kidney injury during ischemic reperfusion process as shown by a significant reduction of urinary inflammatory markers as well as significant reduction of urea and creatinine levels.

1. Introduction

Acute kidney injury (AKI) is a clinical syndrome manifested by significant reduction to renal function which can cause severe azotaemia and often oliguria or anuria [1]. Some studies suggested that small changes in serum creatinine (sCr) and/or urine output (UO) can precipitate the development of serious renal complications if not treated early [2,3]. In order to diagnose AKI, an abrupt decrease in kidney function within a short period of time, which should include both structural damage (tissue injury) and loss of function [1]. This syndrome is quite common worldwide among patients even without critical illness, hence, it is essential that health care professionals can detect it easily [4,5]. Despite the advances in therapeutic techniques, dialysis therapy and renal transplantation, the mortality and morbidity of patients have continued high and have not appreciably improved during the past four decades [6,7].

Diagnosis of AKI can be done via assessing the glomerular filtration rate (GFR). The GFR must be significantly reduced within a short period of time. This is manifested by an acute rise in sCr levels associated with a significant reduction in urine output [8]. Several biochemical markers have been proposed for the diagnosis of AKI which can be used at various stages of disease. However, previous studies could not agree on a single biomarker as the golden standard test to diagnose the disease [9,10].

Recent studies have found that Toll-like receptor 4 (TLR4) signaling contributes to inflammation and development of renal

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diseases through aldosterone induced pathway [11]. TAK-242 is a small cyclohexene derivative molecule that selectively inhibits TLR4 mediated signaling, which may inhibits various kinds of inflammatory mediators such as nitric oxide (NO), tumor necrosis factor (TNF)-α, interleukins and prostaglandin E from lipopolysaccharide (LPS) stimulated macrophages [11–13]. This study aims to clarify if administration of TAK-242 at variable doses may be beneficial in reducing renal I/R injury in a rat model.

2. Methods

2.1. Experimental animals

A total of 35 adult male Sprague-dawely rats weighing 200–300, were included in this study. The study was approved by the Animal Ethics Committee, College of Medicine, University of Kufa. The animals were kept in cages under 12 h light: 12 h dark cycle. Room temperature was kept at 25 °C and humidity at 60–65%, with free access to food and water.

2.2. Study design

Rats were assigned randomly into one of the following five experimental groups ($n = 7$ in each group): Control (I/R) group, Sham (negative control) group, TAK-242 (5 mg/kg body weight) group, TAK-242 (10 mg/kg body weight) group and Vehicle in Dimethyl sulfoxide (DMSO) group.

2.3. Renal I/R procedure

Surgical induction of renal I/R injury was performed as per Hesketh et al. study [14]: Rats were intraperitoneally anesthetized with 100 mg/kg ketamine and 10 mg/kg xylazine [15]. Then, after anesthesia, midline hair area was shaved then abdominal incision was made and right renal nephrectomy and the renal pedicle was dissected unilaterally. A vascular clamp was placed on left renal pedicle for 30 min. After clamp was released, the incision was closed in two layers with 3–0 sutures and rats were returned back to their cages and left for 3 h for reperfusion.

2.4. Biochemical analysis

At the end of experiment both blood and tissue samples were obtained as following:

1. Blood samples: Three milliliters (ml) of blood were collected from the heart and placed into two test tubes. One ml placed in an EDTA test tube and 2 ml placed in a plane tube. Blood samples were allowed to clot at 37 °C and centrifuged at 3000 rpm for 10 min; Sera were removed, and analyzed to determine serum

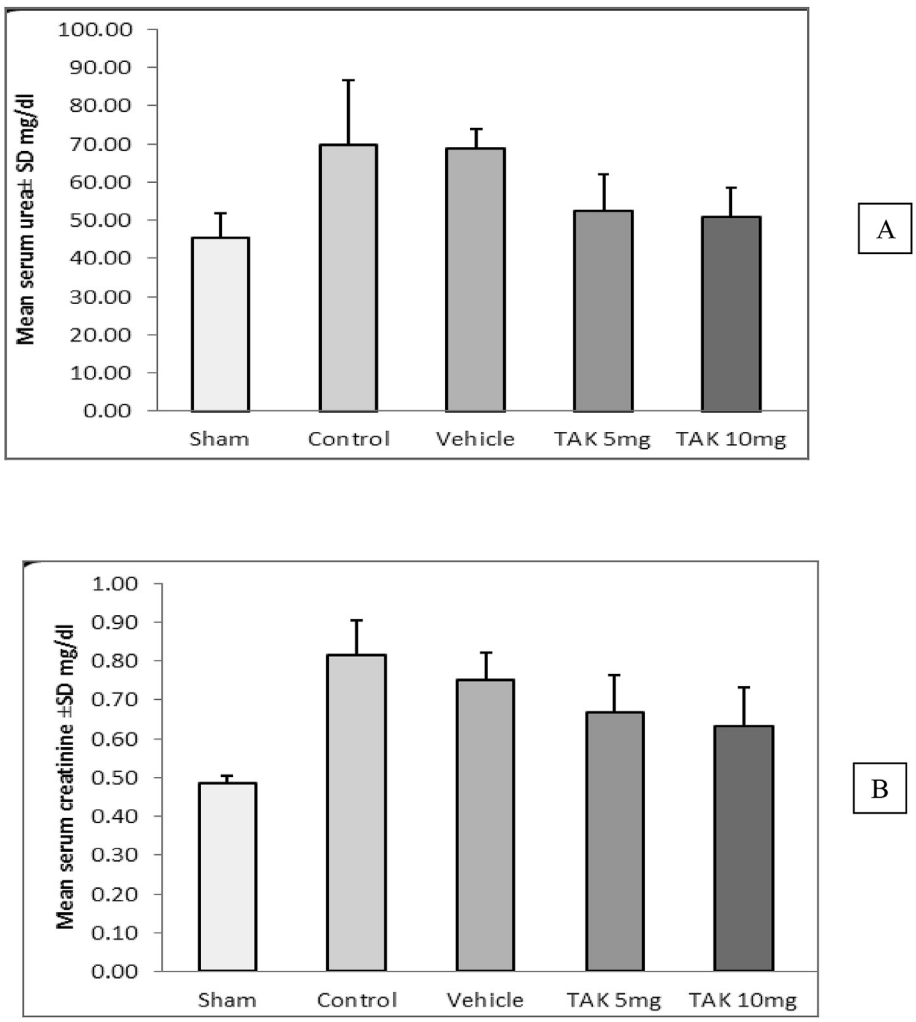

Fig. 1. A: Mean serum urea levels in mg/dl among the five study groups. **B**: Mean serum creatinine levels in mg/dl among the five study groups.

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