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ORIGINAL ARTICLE

Protection against renal ischaemia/reperfusion injury: A comparative experimental study of the effect of ischaemic preconditioning vs. postconditioning

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KEYWORDS

Preconditioning;
Postconditioning;
Ischaemia/reperfusion;
Rat;
Oxidative stress

ABBREVIATIONS

Ipre, ischaemic preconditioning; Ipost, ischaemic postconditioning; I/R, ischaemia/reperfusion; BUN, blood urea nitrogen;

Abstract ***Objective:*** To compare the effect of ischaemic preconditioning (Ipre) vs. ischaemic postconditioning (Ipost) on renal ischaemia/reperfusion (I/R) injury in rats.

Materials and methods: In all, 120 male Sprague–Dawley rats were classified into four groups of 30 rats each, designated sham, control, Ipre and Ipost. Renal function, including serum creatinine, blood urea nitrogen (BUN), creatinine clearance (CrCl), fractional Na excretion (FENa) and renal histopathology were measured at 2, 24 and 48 h after ischaemia. Markers of lipid peroxidation (malondialdehyde, MDA), superoxide dismutase (SOD) and reduced glutathione (GSH) were measured in kidney tissues during the same intervals.

Results: Ipre caused a significant improvement in renal function, as indicated by a significant decrease in serum creatinine, BUN and FENa, with a significant increase in CrCl. However, Ipost caused no significant improvement in renal function. Morphologically Ipre caused a marked significant improvement in the renal tubular

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CrCl, creatinine clearance; FENa, fractional Na excretion; MDA, malondialdehyde; SOD, superoxide dismutase; GSH, reduced glutathione; ROS, reactive oxygen species; H&E, haematoxylin and eosin; OSOM, outer stripe of the outer medulla

damage score compared to Ipost. Also, Ipre caused a significant decrease in MDA, and significant increase in GSH and SOD when compared to Ipost.

Conclusion: Ipre is more potent than Ipost for improving the renal injury induced by I/R. Ipre caused a marked improvement in renal function and morphology, while Ipost caused a minimal improvement in morphology only. Moreover, Ipre caused a marked and significant reduction in oxidative stress in kidney tissues, while Ipost caused a minimal reduction.

Introduction

Renal ischaemia/reperfusion (I/R) injury is a common cause of acute renal failure and contributes to considerable morbidity associated with surgery and anaesthesia [1,2]. Although several decades of research have greatly improved the understanding of the mechanisms underlying renal I/R injury, effective drugs for treating it are still unavailable. Therefore, it is necessary to actively explore other approaches for this problem. Ischaemic preconditioning (Ipre), a well-established phenomenon that describes tissue adaptation to stress by exploiting intrinsic defence mechanisms, was initially described in the heart by Murry et al. [3] and Ambros et al. [4]. Ipre consists of transient periods of non-lethal ischaemia before a subsequent lethal episode of ischaemia. In 2003, Zhao et al. [5], introduced the concept of ischaemic postconditioning (Ipost), which consists of one or more short cycles of reperfusion followed by one or more short cycles of ischaemia, immediately after an ischaemic phase and before the permanent reperfusion.

The efficacy of the protective effect of Ipre and Ipost is variable. In the heart, some studies showed no statistically significant difference in the reduction of infarct size for Ipre and Ipost [5], while other studies showed Ipre to be more effective than Ipost [6]. The differences between the efficacy of these cardioprotective methods might suggest differing underlying protective mechanisms. In the small intestine, dos Santos et al. [7] recently concluded that Ipre and Ipost were equally able to minimise the tissue injury in the intestines of rats subjected to mesenteric ischaemia and reperfusion. In the kidney, several studies reported the beneficial effect of Ipre [8–11] and Ipost [12,13] on renal I/R injury in different species of animal. Nevertheless, to the best of our knowledge, no study has been designed to compare the magnitude of the renoprotective effects of Ipre and Ipost against renal I/R injury. Thus the aim of the present study was to compare the efficacy of Ipre and Ipost in protecting against renal I/R injury in a rat model, for both renal function and renal morphology, and to compare their effects on the redox state in kidney tissue.

Materials and methods

The study included 120 male Sprague–Dawley rats (body weight 200–250 g, 4–6 months old) that were bred in the animal research facility in the Urology & Nephrology Centre at Mansoura, Egypt. Experiments were performed according to the Guide for the Care and Use of Laboratory Animals (Institute for Laboratory Animal Research, National Research Council, Washington, DC: National Academy Press, No. 85–23, revised 1996). All protocols were approved by our ethical committee of Mansoura, Faculty of Medicine.

Study design

The rats were randomly divided into four equal groups: (1) sham, where rats were subjected to right nephrectomy and exposure of the left renal pedicle with no ischaemia; (2) controls, subjected to right nephrectomy and left renal ischaemia for 45 min (definitive ischaemia); (3) Ipre, treated as the control group, but preconditioning ischaemia was induced before the definitive ischaemia; (4) Ipost, treated as the control group, but Ipost was induced after the definitive ischaemia. Each group was subdivided into three subgroups each contains 10 rats, that were killed humanely at 2, 24 and 48 h, respectively, according to the designated subgroup, and the kidneys harvested. Blood and urine samples were collected just before the death. Urine could not be collected at the 2-h sample time.

Experimental model

For the sham operation the rats were anaesthetised with a mixture of ketamine 75 mg/kg and diazepam 5 mg/kg intraperitoneally. After inducing anaesthesia a midline laparotomy was made, then a right nephrectomy was done and the left kidney and its pedicle were dissected off the surrounding perirenal fat along the renal surface. The left kidney was exposed for 45 min with no vascular clamping. The abdomen was then irrigated with isotonic saline and the abdominal incision closed by continuous suture using polyglactin 2/0.