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ORIGINAL ARTICLE

Effects of nicorandil on renal function and histopathology in rats with partial unilateral ureteral obstruction

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Abstract To evaluate the effects of nicorandil in a rat kidney model of partial unilateral ureteral obstruction (PUUO). Thirty male rats were randomly divided into three groups as follows: (1) Group 1 (Sham-control), ureters of the rats were manipulated but not ligated; (2) Group 2 (PUUO-untreated), PUUO was performed with two-thirds of the left ureter embedded in the psoas muscle; and (3) Group 3 (PUUO-nicorandil treated). After PUUO was established, nicorandil (15 mg/kg/day) was administered by gastric lavage for 21 days to determine its effects on PUUO-induced histopathological-, functional-, and oxidative stress-induced changes. The serum levels of blood urea nitrogen and creatinine were reduced in Group 3. The level of urinary albumin and the ratio of urinary protein/creatinine were increased in the kidneys of Group 2 but decreased in Group 3. Malondialdehyde value was decreased in Group 3 compared with Group 2. Antioxidant enzyme activities (catalase, superoxide dismutase, and glutathione peroxidase) were decreased in Group 2. Nicorandil treatment caused an increase in these enzyme activities. In Group 3, leukocyte infiltration and tubular dilatation were significantly reduced. Other parameters, such as degeneration of tubular epithelium and fibrosis, also showed a marked improvement in Group 3. Expression of inducible nitric oxide synthase in

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Group 2 and expression of endothelial nitric oxide synthase in Group 3 were significantly elevated. Nicorandil can inhibit renal tubular damage and tubulointerstitial fibrosis by reducing the effects of oxidative stress after PUUO.

Introduction

Obstructive uropathy (OU) is a major cause of chronic renal insufficiency, particularly in infants and children [1,2]. It affects renal morphogenesis, maturation, and growth because of congenital renal maldevelopment [3]. In the most severe cases, this type of renal injury ultimately results in progressive renal tubular atrophy and interstitial fibrosis, with loss of nephrons [4]. Hence, OU accounts for 23% of pediatric cases of renal insufficiency and 50% of pediatric patients with end-stage renal disease undergoing renal transplantation [5].

Although the therapeutic focus has shifted to regenerative cell-based agents, the lack of a comprehensive understanding of the pathogenesis of renal scar formation following injury remains a major challenge to the development of effective therapeutic strategies. Known factors in the pathophysiology of renal obstructive parenchymal injury include renal blood flow impairment, intrapelvic pressure elevation, and vasoactive and inflammatory mediators [6–8]. Recently, it has been suggested that reactive oxygen species (ROS), which are formed during ureteral obstruction, may play a role in this process [9,10].

Nicorandil [N-(2-hydroxyethyl)-nicotinamide nitrate], a vasodilator that acts as a potassium channel opener, is thought to inhibit superoxide anion production by canine neutrophils, which are activated by either phorbol myristate acetate or opsonized zymogen [11]. In a liver perfusion experiment, Naito et al [12] verified that nicorandil had antioxidative action. Recent studies also reported that nicorandil was beneficial in experimental renal disease, including preventing renal injury induced by ischemia–reperfusion [13] and glomerulonephritis [14] in rats. In humans, the pharmacokinetics of nicorandil have been examined in healthy volunteers and patients with impaired renal function [15,16]. However, no studies have examined whether nicorandil could ameliorate partial unilateral ureteral obstruction (PUUO). Furthermore, the specific mechanisms by which nicorandil confers renoprotection are not known. To our knowledge, the protective effects of nicorandil have not been studied in PUUO induced in a rat model. The aim of this study was to evaluate the effects of nicorandil on antioxidant enzyme levels, renal function, and renal histopathology in a rat kidney model of PUUO.

Materials and methods

All surgical and experimental procedures were approved by the Institutional Animal Care and Use Committee of Abant Izzet Baysal University (Bolu, Turkey). Thirty male (age, 8–10 weeks) Sprague-Dawley rats (body weight, 190–210 g) were enrolled. The animals were provided by Experimental Animal Department of Abant Izzet Baysal University. The procedures were performed according to routine animal care guidelines, and all experimental procedures complied with the Guide for the Care and Use of Laboratory Animals (1996). All the animals were housed under the same environmental conditions and fed the same diets. The rats were kept in sawdust-lined cages (47 × 34 × 18 cm; 4 animals/cage) in one room at a constant temperature (22 ± 2°C), with light from 7:00 AM to 7:00 PM and water and food *ad libitum*.

PUUO surgery

Briefly, the rats were anesthetized by an intraperitoneal injection of xylazine (10 mg/kg) and ketamine hydrochloride (100 mg/kg) and placed on a homeothermic table to maintain a core body temperature of 37°C. Following catheterization of the right femoral vein, fluid replacement was performed with 3 mL/kg/hour of lactated Ringer's solution using an infusion pump.

Surgical PUUO was performed according to the method previously described in the literature [6,8]. Briefly, under anesthesia, a midline longitudinal abdominal incision was made to permit access to the left kidney, ureter, and psoas muscle. Then, a 10-mm groove was created in the psoas muscle. A ureter was placed in the muscle groove, and the muscle edges were fitted together by suturing three points with 6/0 polydioxanone sutures. Thus, the ureter lay in a tunnel with proximally and distally acute angles. The abdomen was then closed with 4/0 silk sutures. The rats were randomly divided into three groups.

Group 1 (Sham-control, $n = 10$): The rats underwent laparotomy through the abdominal midline incision, and their ureters were manipulated but not ligated. The rats in this group were used to determine basal values for biochemical and tissue evaluation.

Group 2 (PUUO-untreated, $n = 10$): PUUO was performed, with two-thirds of the left ureter embedded in the psoas muscle through a midline abdominal incision using 6/0 polydioxanone sutures, as described above.

Group 3 (PUUO-nicorandil treated, $n = 10$): After PUUO was established, nicorandil (15 mg/kg/day) was administered by gastric lavage for 21 days to determine its effects on PUUO-induced histopathological-, functional-, and oxidative stress-induced changes.

At the end of the experiment, 24-hour urine samples were collected using metabolic cages. The animals were anesthetized again, blood samples were collected from the abdominal aorta, and the left kidneys were removed for

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