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# The role of renal sympathetic nervous system in the pathogenesis of ischemic acute renal failure

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**Abstract**

We investigated the role of renal sympathetic nervous system in the progression of ischemia/reperfusion-induced acute renal failure in rats. Acute renal failure was induced by clamping the left renal artery and vein for 45 min followed by reperfusion, 2 weeks after the contralateral nephrectomy. Renal venous plasma norepinephrine concentrations markedly and significantly increased immediately after reperfusion, thereafter, the increased level declined but remained higher even at 24 h after reperfusion. Renal sympathetic nerve activity was significantly augmented during the renal ischemia. Renal denervation or the administration of pentolinium, a ganglion blocking agent, (5 mg/kg i.v.) at 5 min before ischemia attenuated the ischemia/reperfusion-induced renal dysfunction and histological damage, such as proteinaceous casts in tubuli and tubular necrosis. The elevation of renal venous norepinephrine levels after reperfusion was suppressed by renal denervation or pentolinium treatment. Thus, a surgical or pharmacological blockade of renal sympathetic nerve prevents the progression of ischemia/reperfusion-induced acute renal failure, thereby suggesting that renal sympathetic nervous system plays an important role in the development of the ischemic acute renal failure.


*Keywords:* Ischemia; Reperfusion; Acute renal failure; Sympathetic nerve; Norepinephrine

## 1. Introduction

Kidneys are abundantly innervated internal organ and the renal sympathetic nerve plays an important role in regulating body fluid volume and blood pressure via the modulation of renal functions (Moss, 1982). The direct renal nerve stimulation produces frequency-dependent renal hemodynamic changes and increases in norepinephrine overflow into the renal vein (Egi et al., 1994; Tadano et al., 1998). Norepinephrine injected into the renal artery of dogs (Cronin et al., 1978) and rats (Conger et al., 1991) causes an ischemic acute renal failure, in which there are continual abnormalities of renal hemodynamics and renal tissue injury, thereby suggesting that activation of renal sympathetic nervous system is involved in the postischemic renal injury.

During the renal ischemia, there is an activation of afferent renal nerve activity, which leads to a reflexive activation of efferent renal sympathetic nerve (Recordani et al., 1978). It has also been suggested that renal sympathetic nerves and circulating catecholamines are considered to be involved in the development of ischemic acute renal failure (Baines, 1983; Iaina and Eliahou, 1983). However, there is no direct evidence indicating that renal sympathetic nervous system and/or norepinephrine overflow from the nerve endings is contributive to the pathogenesis of the ischemia/reperfusion-induced acute renal failure.

Ischemic acute renal failure is a frequent clinical syndrome with high morbidity and mortality (Thadani et al., 1996). Reperfusion of previously ischemic renal tissue initiates a complex cellular events that results in injury and the eventual death of renal cells due to a combination of apoptosis and necrosis (Lieberthal and Levine, 1996). The molecular mechanisms underlying the ischemia/reper-

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fusion-induced renal injury are poorly understood, but it has been reported that several causal factors (ATP depletion, reactive oxygen species, phospholipase activation, neutrophil infiltration, vasoactive peptides, etc.) are contributive to the pathogenesis of this renal damage (Edelstein et al., 1997).

With respect to the relationship between renal sympathetic nervous system and the ischemia/reperfusion-induced acute renal failure, one available experimental evidence is recently reported by Ogawa et al. (2002) who found that renal denervation before the ischemia attenuates the decreased responses of glomerular filtaration rate after the ischemia/reperfusion. In the present study, in order to clarify the pathogenic role of renal sympathetic nervous system and/or norepinephrine overflow from the nerve endings in the pathogenesis of the ischemia/reperfusion-induced renal injury, we determined norepinephrine overflow into the renal vein and renal sympathetic nerve activity during ischemia and reperfusion. We also examined the effect of renal denervation and ganglion blocking agent on the ischemia/reperfusion-induced renal dysfunction and tissue injury.

## 2. Materials and methods

### 2.1. Animals and experimental design

Male Sprague–Dawley rats (10 weeks of age, Japan SLC, Shizuoka, Japan) were used. Animals were housed in a light-controlled room with a 12-h light/dark cycle and were allowed ad libitum access to food and water. Experimental protocols and animal care methods in the experiments were approved by the Experimental Animal Committee at Osaka University of Pharmaceutical Sciences. Two weeks before the study (at 8 weeks of age), the right kidney was removed through a small flank incision under pentobarbital anesthesia (50 mg/kg i.p.). After a 2-week recovery period, these rats were separated into four groups: (1) sham-operated control; (2) untreated or vehicle-treated acute renal failure; (3) renal denervated acute renal failure; and (4) pre-ischemic treatment with pentolinium (5 mg/kg i.v., Sigma, St. Louis, MO) in acute renal failure. To induce ischemic acute renal failure, rats were anesthetized with pentobarbital (50 mg/kg i.p.), and the left kidney was exposed through a small flank incision. The left renal artery and vein were occluded with a nontraumatic clamp for 45 min. At the end of the ischemic period, the clamp was released to allow reperfusion. Renal denervation was accomplished 5 min before the start of ischemia by cutting all visible nerves entering the renal hilus, stripping the renal artery and vein of adventitia, and applying a 10% phenol in 70% ethanol to the vessels (Rudd et al., 1986; Tomoda et al., 1997). Pentolinium or vehicle (0.9% saline) was injected 5 min before the start of ischemia, in a volume of 1 ml/kg into the external jugular vein. In sham-operated control rats, the kidney was treated identically, except for the clamping.

Animals exposed to 45 min ischemia were housed in metabolic cages at 24 h after reperfusion. At the end of urine collection for 5 h, blood samples were drawn from the thoracic aorta, and then the left kidneys were excised under pentobarbital anesthesia (50 mg/kg i.p.). The plasma was separated by centrifugation and used for measurements of renal function parameters. The kidneys were used for light microscopic observation.

In separate experiments, we examined effects of renal denervation or pentolinium treatment (5 mg/kg i.v.) on changes of norepinephrine level in renal venous plasma after reperfusion. Under pentobarbital (50 mg/kg i.p.) anesthesia, an abdominal midline incision of uninephrectomized rats was made and the left kidney was exposed. A curved 26-gauge needle connected to a polyethylene catheter was inserted into the left renal vein for venous blood sampling, and each sample was taken at baseline, immediately after the reperfusion and at 15 min, 6 h or 24 h after reperfusion following 45-min ischemia, respectively. The sampling period (only one sample from each animal) was 2 min in duration. Plasma was immediately separated by centrifugation. These samples were stored at $-20$ °C until the assay for norepinephrine concentration.

As described below, using other rats, electrical signals of renal neural activity were directly recorded for evaluation of changes in renal sympathetic nerve activity during 45-min ischemic period.

### 2.2. Histological studies

Excised left kidneys were processed for light microscopic observation, according to standard procedures. The kidneys were then preserved in phosphate-buffered 10% formalin, after which the kidneys were chopped into small pieces, embedded in paraffin wax, cut at 3 μm and stained with hematoxylin and eosin. Histopathological changes were analyzed for proteinaceous casts in tubuli and tubular necrosis, as suggested by Solez et al. (1974). These were graded as follows: no damage (0); mild (1, unicellular, patchy isolated damage); moderate (2, damage less than 25%); severe (3, damage between 25% and 50%); and very severe (4, more than 50% damage). Evaluations were made in a blind manner.

### 2.3. Analytical procedures

Blood urea nitrogen and creatinine levels in plasma or urine were determined using commercial kits, the BUN-test-Wako and Creatinine-test-Wako (Wako, Osaka, Japan), respectively. Urinary osmolality was measured by freezing point depression (Fiske Associates, Norwood, MA). Urine and plasma sodium concentrations were determined using a flame photometer (Hitachi, 205D, Hitachinaka, Japan). Fractional excretion of sodium

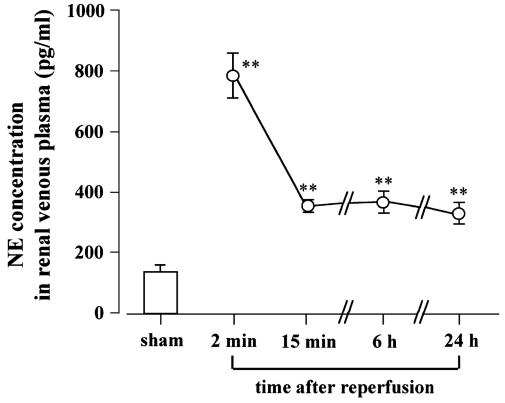


Fig. 1. Norepinephrine (NE) concentrations in renal venous plasma of ischemia/reperfused and sham rats. Blood samples (one sample from each animal) of ischemia/reperfused rat were taken during 2 min at indicated time points. Values are means ± S.E.M. ($n = 6$). **$P < 0.01$, compared with sham-operated rats.

($FE_{Na}$) was calculated from the following formula: $FE_{Na} = U_{Na}V/(P_{Na} \times \text{creatinine clearance}) \times 100$, where $U_{Na}V$ is urinary excretion of sodium and $P_{Na}$ is the plasma sodium concentration. Norepinephrine concentration in renal venous plasma was measured by high-performance liquid chromatography with an amperometric detector (EC-100, EICOM, Kyoto, Japan), as previously reported (Hayashi et al., 1991).

### 2.4. Renal nerve recording

Renal sympathetic nerve activity was recorded from the left renal nerve branch as previously described by Shokoji et al. (2003). The nerve was isolated near the aortic–renal arterial junction through a left flank incision and placed on a Teflon-coated stainless-steel bipolar electrode. The renal nerve and electrode were covered with silicone rubber. The renal nerve discharge was amplified using a differential amplifier (AVB-10, Nihon Kohden, Osaka, Japan) with a band-pass filter (low frequency 50 Hz, high frequency 1 kHz). The amplified and filtered signal was visualized on a dual-beam oscilloscope (VC-10, Nihon Koden) and monitored by an audio speaker. The output from the amplifier was integrated by an integrator (Nihon Denki Sanei 1322, Osaka, Japan) with 1-s resetting. The output from the integrator was displayed on a polygraph system recorder (Nihon Denki Sanei 8M14). For the quantification of renal sympathetic nerve activity, the height of integrated nerve discharge was measured for 30 s in each experiment. The changes in nerve activity were expressed as percentages of control resting spontaneous nerve activity.

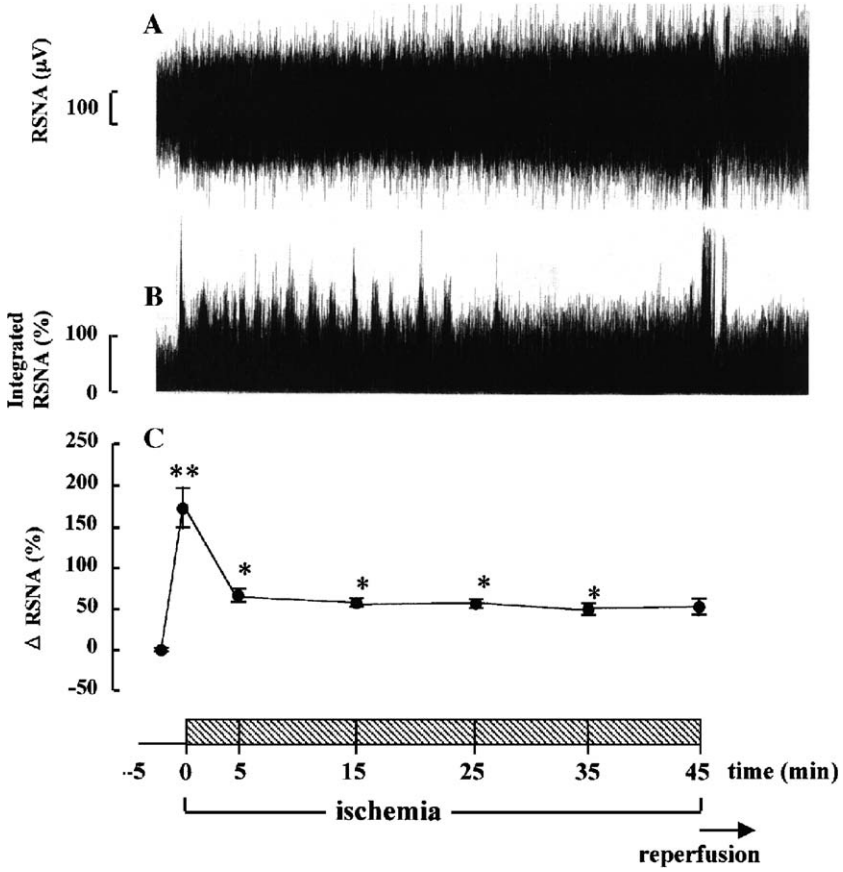


Fig. 2. Changes in renal sympathetic nerve activity (RSNA, A) and integrated RSNA (B) to 45-min ischemia. (C) Percent change from basal. Each point and bar represents the mean ± S.E.M. ($n = 5$). *$P < 0.05$ and **$P < 0.01$, compared with the pre-ischemic value.

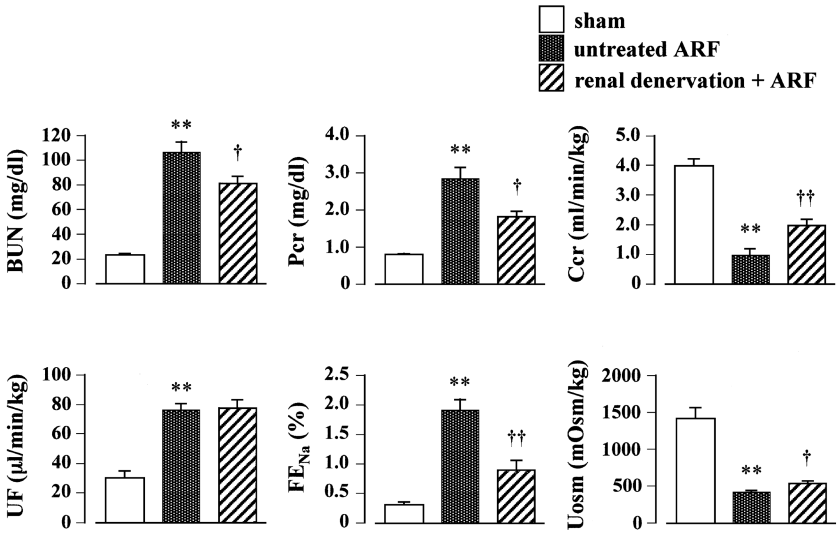


Fig. 3. Effects of renal denervation on blood urea nitrogen (BUN), plasma creatinine concentration (Pcr), creatinine clearance (Ccr), urine flow (UF), fractional excretion of sodium ($FE_{Na}$) and urinary osmolality (Uosm) at 24 h after reperfusion. Each column and bar represents the mean ± S.E.M. ($n=6$). **$P<0.01$, compared with sham-operated rats. $^{\dagger}P<0.05$, $^{\dagger\dagger}P<0.01$, compared with untreated ARF rats. ARF, acute renal failure.

During the experiment, the femoral arterial catheter was connected to a Statham pressure transducer (P23 ID). The systemic blood pressure and heart rate were continuously recorded in a multichannel polygraph (Nihon Denki Sanei 360). Heart rate triggered by the blood pressure pulse was measured with a cardiotachometer (Nihon Denki Sanei 1321).

### 2.5. Statistical analysis

Values were expressed as means ± S.E.M. For statistical analysis, we used one-way analysis of variance combined with Dunnett's or Bonferroni's multiple comparison tests. Histological data were analyzed using the Mann–Whitney test. Data in nerve recording studies were analysed by repeated measures using one-way analysis of variance followed by Dunnett's multiple range test. For all comparisons, differences were considered significant at $P<0.05$.

## 3. Results

### 3.1. Norepinephrine concentration in renal venous plasma after ischemia/reperfusion

As shown Fig. 1, norepinephrine concentration in renal venous plasma obtained from animals immediately (within 2 min) after the reperfusion following 45-min ischemia, was remarkably increased, compared with that seen in sham-

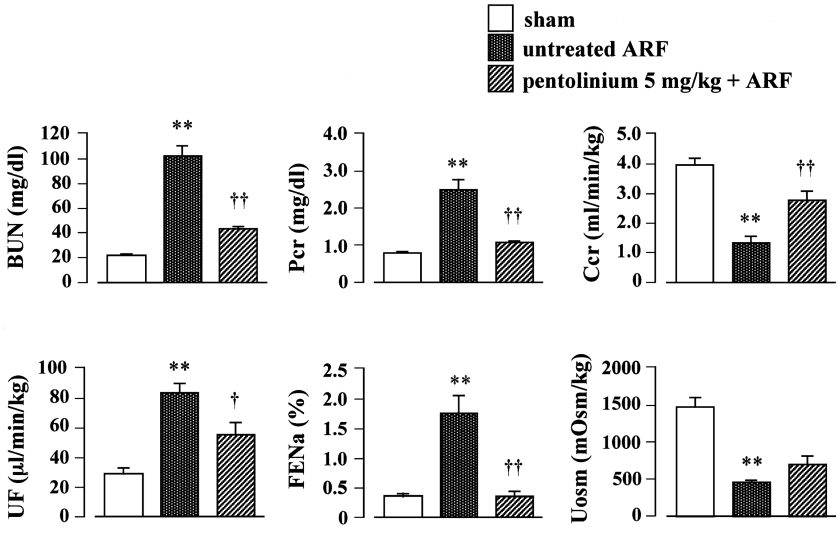


Fig. 4. Effects of ganglionic blockade with pentolinium on blood urea nitrogen (BUN), plasma creatinine concentration (Pcr), creatinine clearance (Ccr), urine flow (UF), fractional excretion of sodium ($FE_{Na}$) and urinary osmolality (Uosm) at 24 h after reperfusion. Each column and bar represents the mean ± S.E.M. ($n=6$). **$P<0.01$, compared with sham-operated rats. $^{\dagger}P<0.05$, $^{\dagger\dagger}P<0.01$, compared with untreated ARF rats. ARF, acute renal failure.

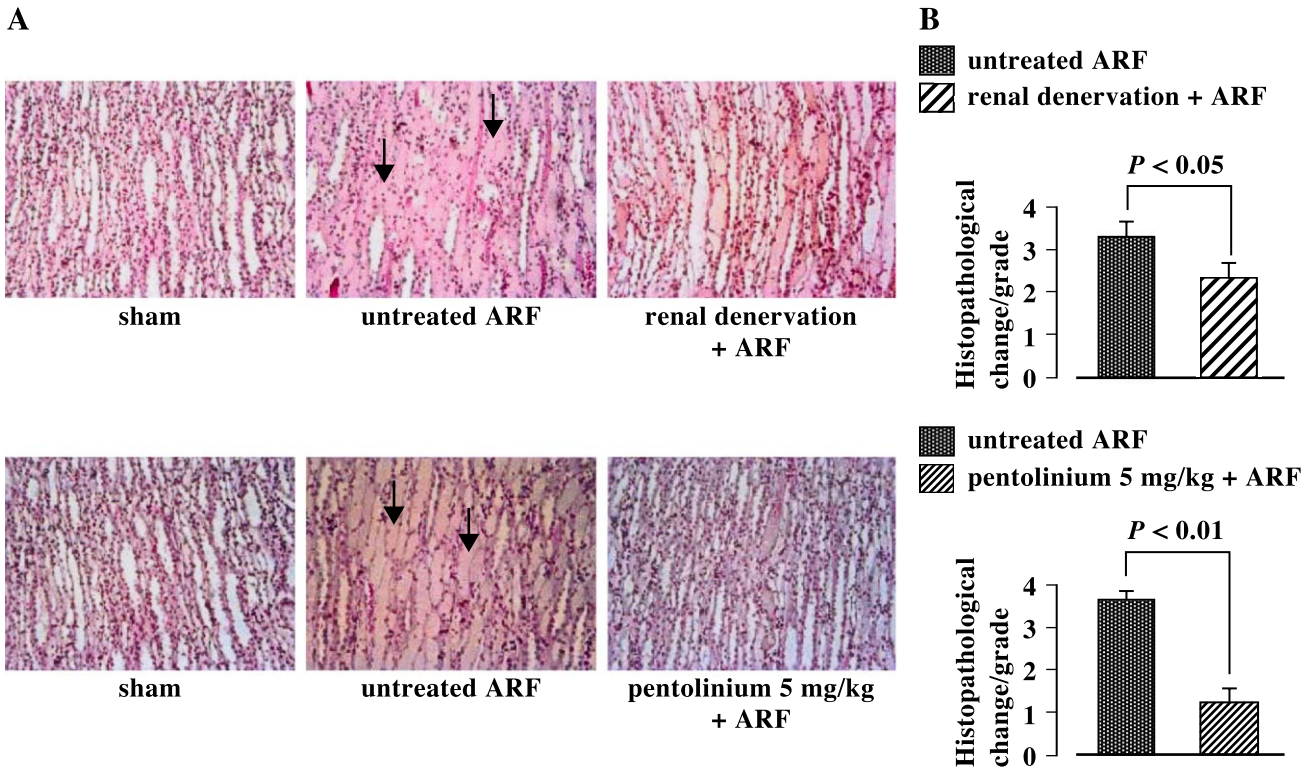


Fig. 5. Light microscopy (A) of the inner zone of medulla of the kidney with and without renal denervation or pentolinium treatment, at 24 h after reperfusion and sham rat. Arrows indicate proteinaceous casts in tubuli (hematoxylin and eosin staining, magnification, × 200). (B) Histopathological change/grade. Each column and bar represents the mean ± S.E.M. ($n = 6$). Grades: no damage (0), mild (1), moderate (2), severe (3), very severe (4).

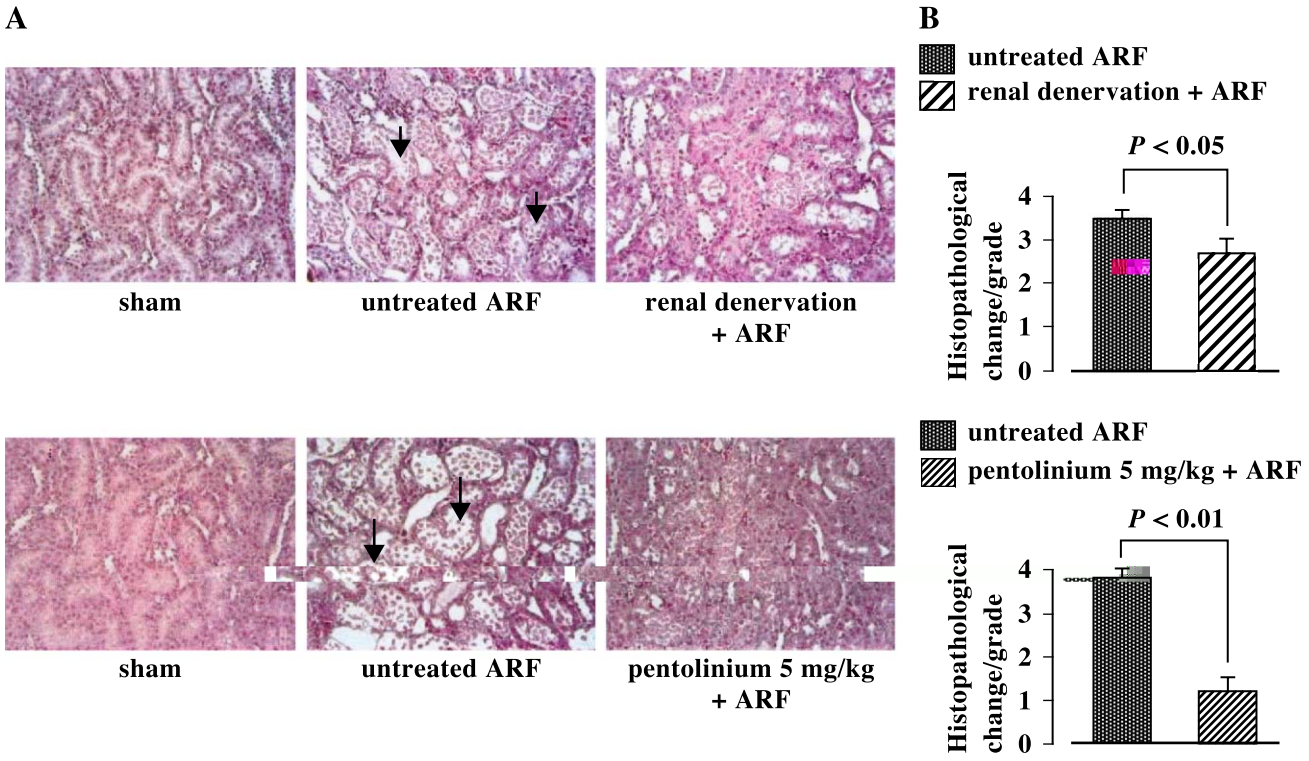


Fig. 6. Light microscopy (A) of the outer zone outer stripe of medulla of the kidney with and without renal denervation or pentolinium treatment, at 24 h after reperfusion and sham rat. Arrows indicate tubular necrosis (hematoxylin and eosin staining, magnification, × 200). (B) Histopathological change/grade. Each column and bar represents the mean ± S.E.M. ($n = 6$). Grades: no damage (0), mild (1), moderate (2), severe (3), very severe (4).

operated control animals. Thereafter, the increased level rapidly declined 15 min after the reperfusion but remained higher even 24 h after reperfusion.

### 3.2. Responses of renal sympathetic nerve activity to the 45-min ischemia

The typical responses of renal sympathetic nerve activity to the 45-min ischemia are shown in Fig. 2A and B. Immediately after the start of ischemia, integrated renal sympathetic nerve activity was markedly increased, and about 170% increase was observed. Thereafter, increased level somewhat declined, but significant increases lasted throughout 45-min ischemic period, compared with the basal (Fig. 2C).

### 3.3. Renal function after the ischemia/reperfusion and effects of renal denervation or ganglionic blockade

Renal function of rats subjected to 45-min ischemia showed a marked deterioration when measured 24 h after the reperfusion. As compared with sham-operated rats, untreated acute renal failure rats showed significant increases in blood urea nitrogen, plasma creatinine concentration, urine flow and fractional excretion of sodium, and significant decreases in creatinine clearance and urinary osmolality. Renal denervation 5 min before the start of ischemia significantly improved the ischemia/reperfusion-induced renal dysfunction, except for urine flow (Fig. 3). Qualitatively similar results were observed by the pre-ischemic treatment with pentolinium, at a dose of 5 mg/kg, and the ameliorating effects were much more efficient, compared with cases of renal denervation (Fig. 4).

### 3.4. Histological renal damage after the ischemia/reperfusion and effects of renal denervation or ganglionic blockade

Histopathological examination revealed severe lesions in the kidney of untreated acute renal failure rats. These changes were characterized by proteinaceous casts in tubuli in the inner zone of medulla (Fig. 5) and tubular necrosis in the outer zone outer stripe of medulla (Fig. 6). Renal denervation or ganglionic blockade with pentolinium significantly attenuated the development of these lesions, and the latter case was more efficient (Figs. 5B and 6B). Typical photographs are shown in Figs. 5A and 6A.

### 3.5. Effects of renal denervation or ganglionic blockade on the elevation of norepinephrine concentration in renal venous plasma after the ischemia/reperfusion

As shown in Fig. 7, increases in norepinephrine concentration in renal venous plasma observed immediately and at 24 h after the reperfusion were significantly suppressed by renal denervation. The pre-ischemic treatment with pentolinium also significantly but somewhat efficiently suppressed the increased norepinephrine levels.

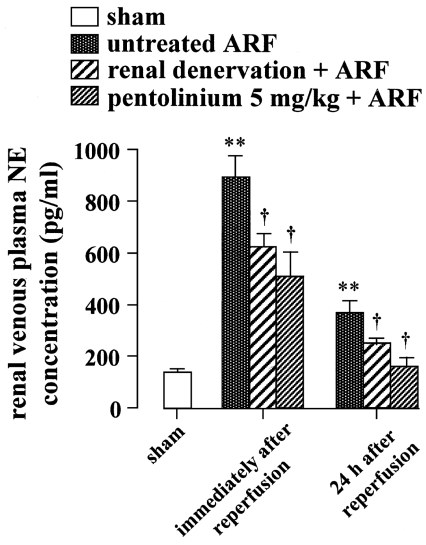


Fig. 7. Effect of renal denervation or pentolinium treatment on norepinephrine (NE) concentrations in renal venous plasma of ischemia/reperfused rats. Blood samples (one sample from each animal) of ischemia/reperfused rats were taken during 2 min at indicated time points. Values are means ± S.E.M. ($n=6$). $^{**}P<0.01$, compared with sham-operated rats. $^{\dagger}P<0.05$, compared with untreated ARF rats. ARF, acute renal failure.

## 4. Discussion

Renal sympathetic nerves and circulating cathcholamines are considered to be involved in the development of acute renal failure (Baines, 1983; Iaina and Eliahou, 1983). Intrarenal arterial infusion of norepinephrine is known to produce ischemic acute renal failure by constricting renal vasculature (Conger et al., 1991). α-Adrenoceptor antagonist phenoxybenzamine was reported to improve mercury-induced reductions in renal blood flow and glomerular filtration rate (Solomon and Hollenberg, 1975). The authors suggested the possible involvement of increased release of endogenous catecholamines in mercury-induced renal dysfunction. $\alpha_2$-Adrenoceptor agonist clonidine (Solez et al., 1980) and β-adrenoceptor antagonist propranolol (Solez et al., 1977; Chevalier and Finn, 1980) are also known to lessen postischemic acute renal failure. Recently, it has been reported that renal denervation is protective against endotoxemia-induced acute renal failure (Wang et al., 2002). Also, Ogawa et al. (2002) found that renal denervation before the ischemia attenuates the decreased responses of glomerular filtaration rate after the ischemia/reperfusion. These findings support the view that norepinephrine released from renal sympathetic nerves is closely related to the pathogenesis of ischemia- and drug-induced renal injuries. However, there is no direct evidence on the relationships between the renal sympathetic nervous system and the postischemic acute renal failure.

In the current study, we obtained evidence that norepinephrine overflow into renal vein was markedly increased immediately after the reperfusion following 45-min ischemia and increased level lasted for 24 h after the reperfusion. We also found that the increases in the norepinephrine overflow were suppressed by renal denervation or pharmacological ganglionic blockade with pentolinium. Integrated renal sympathetic nerve activity was enhanced during the 45-min ischemic period, although the most notable activation was observed just after the start of ischemia. These findings strongly suggest that both the ischemia itself and the reperfusion stimulate the renal sympathetic nervous system and augment the transmitter release from nerve endings. Furthermore, the ischemia/reperfusion-induced renal dysfunction and tissue injury were efficiently improved by renal denervation or pre-ischemic pentolinium treatment. Taken together, it seems likely that endogenous norepinephrine released from renal sympathetic nerve endings plays an important role in the development of ischemia/reperfusion-induced acute renal failure.

In this study, we utilized two methods, renal denervation and ganglionic glockade, in order to exclude the involvement of renal sympathetic nerves in the ischemic acute renal failure. Protective efficacies against the postischemic renal dysfunction and tissue injury are considerably better in the latter cases than in the former. Suppressive actions on norepinephrine overflow into renal vein were also somewhat efficient in pentolinium-treated animals. The reason for the difference in efficacies are unclear, but rather these results support the importance of norepinephrine overflow in the pathogenesis of postischemic renal injury. One possibility on the mechanisms behind the marked protective effect of pentolinium is that the agant can systemically suppress the sympathetic nervous system, whereas the effect of renal denervation is probably limited to the kidney. In other words, the ganglionic blockade would suppress the norepinephrine overflow derived from extrarenal organs (e.g., heart), which may be partly contributive to the postischemic renal injury. The monitoring of arterial plasma norepinephrine concentrations may clarify the above problem.

Oliver et al. (1980) pointed out that norepinephrine overflow into the renal vein could be useful to assess the activity of renal sympathetic nervous system, since there was a significant linear relationship between the frequency of stimulation and norepinephrine concentrations in renal venous plasma, when renal nerves were electrically stimulated in anesthetized dogs. On the other hand, Deka-Starosta et al. (1989) demonstrated using anesthetized rats that reflexive changes in directly recorded renal sympathetic nerve activity in response to blood pressure changes, positively correlated with those in renal spillover of norepinephrine. Consistent with the above findings, the present results confirm that renal sympathetic nerve activity is enhanced by the ischemia and simultaneously norepinephrine release from renal sympathetic nerves is augmented during ischemia and the following reperfusion.

The renal nerves are mixed nerves that contain both afferent and efferent nerve fibers, the former modulates neurotransmission toward central nervous system and the latter modulates renal function and hemodynamics. The efferent renal innervation is composed of postganglionic sympathetic fibers that typically exert their effects through release of norepinephrine onto the postsynaptic adrenoceptors (Moss, 1982). Recordani et al. (1978) originally found that during renal ischemia, there is activation of afferent renal nerve activity. These authors suggest that this activation is probably mediated by a renal chemoreceptors. It is known that electrical stimulation of afferent renal nerves results in a reflex excitation of both ipsilateral and contralateral efferent renal nerves (renorenal reflexes) (Calaresu et al., 1978). In the present study, we also observed that the renal sympathetic nerve activity during renal ischemia was attenuated by the nerve section distal to the electrode (unpublished observation). Thus, it is reasonable to consider that renal ischemia itself activates renal afferent nerves and causes a reflexive activation of efferent nerves, which is followed by norepinephrine spillover from the nerve endings of the postischemic kidney.

It is well known that the decrease of oxygen supply by ischemia causes ATP depletion and intracellular acidosis due to lactate production. In sympathetic nerve endings of ischemic hearts, free axoplasmic norepinephrine massively accumulates due to incapability of the driving force for norepinephrine storage because its vesicular storage depends on $H^+$ gradient and ATP in physiological conditions. An increase in axoplasmic $H^+$ activates $Na^+/H^+$ exchanger, consequently leading to an influx of $Na^+$ in exchange for $H^+$. Furthermore, inhibition of $Na^+/K^+$ ATPase activity by ATP depletion results in accumulation of axoplasmic $Na^+$. This $Na^+$ accumulation triggers an excessive axoplasmic norepinephrine release via a reversal of norepinephrine transporter from intracellular space to extracellular space (Schömig et al., 1988). It has been considered that, in protracted myocardial ischemia, this carrier-mediated norepinephrine release is the major mechanism for the norepinephrine overflow from the nerve endings (Schömig, 1990). It is unclear whether the above view is applicable to renal ischemia. However, the present results that decreasing effects of renal denervation or ganglionic blockade on norepinephrine overflow from ischemic kidney were only partial, leads us to need further studies.

Although the ameliorating effects of renal denervation or pharmacological ganglionic blockade on ischemia/reperfusion-induced renal injury were incomplete, our findings strongly suggest that renal sympathetic nervous system plays an important role in the development of ischemic acute renal failure. Ischemia/reperfusion-induced renal injury is unavoidable insult in the case of renal transplantation using non-heart beating donors or donors with an unstable hemodynamic status. Thus, the possibility whether the enhancement of renal sympathetic nervous system is responsible for the allograft dysfunction, warrants further attention.

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