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Prior Ischemic Treatment Renders Kidney Resistant to Subsequent Ischemia

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ABSTRACT

Prior ischemia leads to resistance against subsequent ischemic insults. The mechanisms that underlie this adaptive response remain unidentified. Thus, we studied whether the reduced susceptibility of mice previously subjected to the ischemia to ischemia/reperfusion injury is related with altered inflammatory responses. Thirty minutes of bilateral kidney ischemia results in significantly increased plasma creatinine and blood urea nitrogen levels in BALB/c male mice. There is severe disruption of actin cytoskeleton of proximal tubular cells in the outer stripe of the outer medulla 24 hours post-ischemia. When mice are subjected to 30 minutes of bilateral ischemia 8 days later, there is no increase in plasma creatinine and blood urea nitrogen levels and the post-ischemic disruption of actin cytoskeleton of proximal tubular cells is much less. Inflammatory responses have highly implicated with ischemia/reperfusion injury. Ischemia results in the increased tissue myeloperoxidase (MPO) activity that is a marker of leukocyte infiltration. There is, however, no the post-ischemic increase of MPO activity in kidneys previously subjected to ischemia. Post-ischemic expression of tissue intercellular adhesion molecule-1 (ICAM-1) is greater in the kidney previously sham-operated than in the kidneys previously subjected to ischemia. In conclusion, prior ischemia protects kidney function and morphology against subsequent ischemia 8 days later. The resistance is associated with the reduced post-ischemic leukocyte infiltration due to the reduced post-ischemic ICAM-1 expression.

Key words : Ischemia, Inflammation, Intercellular adhesion molecule-1, Kidney, Myeloperoxidase

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Introduction

Prior ischemic insult renders organs resistant to subsequent ischemia (1-5). We have previously reported that prior ischemia or ureteral obstruction prevents kidney against subsequent ischemia in the mouse kidney (6, 7). The mechanisms that underlie this adaptive response remain unidentified. Neutrophils are recruited to the sites of inflammation and play important roles in defense against infectious microorganisms by releasing superoxide and related radicals and enzymes such as proteases (8, 9). However, the excessive presence of these cells often augments injury by damaging surrounding normal tissues. Infiltration of neutrophils has been correlated with ischemia/reperfusion injury of several organs (10-12). Reduction of renal blood flow is one of important factors in post-ischemic acute renal failure (13). The reduction of renal blood flow is affected by results of inflammatory reactions such as endothelial dysfunction, leukocyte adhesion, and leukocyte-endothelial adhesion (14, 15). Considerable evidence suggests that inhibition of the inflammatory reaction reduce the perturbation of renal blood flow and the tubular dysfunction induced by ischemia/reperfusion (16, 17). We previously reported that prior transient ureteral obstruction renders the kidney resistant to ischemia and that the kidney has reduced post-ischemic leukocyte infiltration (6). Post-ischemic tissues generate inflammatory mediators and upregulate leukocyte-endothelial adhesion molecules, such as ICAM-1 which can attract and/or activate leukocytes, potentiate small vessel occlusion, and promote further production of inflammatory mediators. Thus, we studied whether the reduced susceptibility of mice previously subjected to the ischemia to ischemia/reperfusion injury is related with altered inflammatory responses. Our findings reveal that the kidneys previously exposed to ischemia are much less susceptible to subsequent ischemia than the kidneys previously sham-operated. This reduced injury is correlated with less leukocyte infiltration and lower post-ischemic ICAM-1 expression.

Methods

Animal preparation

All experiments were performed in male BALB/c mice

(Charles River Laboratory) weighing 20-25g. Mice were allowed free access to water and standard mice chow. Blood was drawn and a baseline level of serum creatinine determined. Animals were anesthetized with pentobarbital sodium (50 mg/kg, ip) and administered 1 ml of 0.9 % NaCl (37℃) on the day of surgery (day 0). Body temperature was maintained at 36-38℃. Kidneys were exposed through flank incisions. Animals were divided into 4 groups (Table 1). On day 0, mice were subjected to 30 minutes of bilateral renal ischemia by clamping both renal pedicles with non-traumatic microaneurysm clamps (preconditioned; Roboz). Some animals underwent sham surgery (non-preconditioned). The incisions were temporarily closed during ischemia or sham surgery. After 30 minutes the clamps were removed and reperfusion of the kidneys was visually confirmed. Animals were exposed to 30 minutes of either bilateral ischemia or sham surgery on day 8.

Kidneys were harvested at indicated times on Figures. Kidneys were snap frozen in liquid nitrogen to use Western analysis or MPO activity, or were rinsed in phosphate buffered saline (PBS), and fixed in 4% paraformaldehyde for histological analysis.

Renal functional parameters

Seventy microliters of blood were taken from the retroorbital vein plexus at the times indicated on the Figures. Plasma creatinine or blood urea nitrogen (BUN) concentration was measured using a Beckman Creatinine Analyzer II or a spectrophotometer, respectively.

Immunocytochemistry

Sections were prepared from kidney fixed with 4% paraformaldehyde and were stained with phalloidin, which stains the actin cytoskeleton, or ICAM-1 as previously described(16, 18). Fluorescein isothiocyanate-labeled phalloidin (Phalloidin; 1:100) was obtained from Sigma(st. Ldlis, MO). Kidneys were perfused via the left ventricle with 30 ml of PBS for 2 minutes at 37℃ and then PLP (4% paraformaldehyde-75 mM L-lysine-10 mM sodium periodate) fixative. Kidneys were excised and placed in PLP overnight at 4℃. Kidneys were then washed and stored in PBS containing 0.02% sodium azide at 4℃. Fixed tissue was washed with PBS three times for 5 minutes each, placed overnight in PBS containing 30% sucrose, embedded in oxytetracycline compound (Sakura FineTek, Torrance, CA), frozen in liquid nitrogen, and then cut into 5㎛ sections using a cryotome. Sections were mounted on Fisher Superfrost Plus (Fisher LA, USA) microscope slides, dried in air and stored at -20℃.

For staining with phalloidin which stains actin cytoskeleton, sections were incubated in blocking buffer containing FITC-labelled phalloidin for 20 minutes at room temperature, washed three times in PBS for 5 minutes each and mounted with a 1:1 mixture of Vectashield (Vector Laboratories LA, USA) and 0.3 M Tris HCl, pH 8.9.

To detect ICAM-1, sections were dried, incubated in PBS containing 0.1% SDS for 5 minutes, washed in PBS for 10 minutes, and incubated in blocking buffer (PBS containing 2% BSA) for 20 minutes at room temperature. Sections were then incubated with antibody to ICAM-1, diluted in blocking buffer in a humidified chamber for 1 hour at room temperature. Sections were washed with PBS twice for 5 minutes each, with PBS containing 1.9% NaCl (high salt PBS) for 5 minutes and with PBS for 5 minutes. For negative controls, primary antibody was replaced with blocking buffer.

Secondary antibodies were diluted in blocking buffer and placed on sections for 1 hour at room temperature, then washed twice in high salt PBS, once in PBS and mounted as described above. Images were viewed on a Nikon FXA epifluoescence microscope and collected using a digital camera (Hamamatusa Digital Camera).

Myeloperoxidase (MPO) activity

MPO activity, an index of tissue leukocyte infiltration, was measured in 24 hours post-ischemic kidney as previously described(6). Activity was normalized to protein concentration.

Western Blot Analysis.

Immunoblot were performed as previously described(7). ICAM-1 antibody was obtained from M.A. Arauot (Massachusetts General Hospital).

Statistical analysis

All results were expressed as mean ± S.E.M. The difference between two mean values was analyzed by ANOVA. A $p<0.05$ was taken as statistically significant.

Table 1. Animal groups and procedures

Groups	n	Initial procedure (day 0)	Second procedure (day 8)
I	7	Sham bilateral ischemia	Sham bilateral ischemia
II	7	Sham bilateral ischemia	Bilateral ischemia
III	7	Bilateral ischemia	Sham bilateral ischemia
IV	7	Bilateral ischemia	Bilateral ischemia

On day 0, animals were subjected to either 30 minutes of bilateral renal ischemia (preconditioned) or sham surgery (non-preconditioned) on day 0. Eight days after the first surgery, the animals were exposed to either 30 minutes of bilateral ischemia or sham-operation.

Each group consisted of 7 animals as indicated in the Table 1.

Results

Prior ischemia preserves renal function and morphology from subsequent ischemia/reperfusion insult

Renal ischemia/reperfusion results in severe loss of renal function. There are no changes of plasma creatinine and BUN levels on animals 24 hours after sham operation (Fig. 1). Thirty minutes of bilateral ischemia significantly increases the levels of plasma creatinine and BUN in the Group II animals (which is non-preconditioned). In the Group IV (which is preconditioned), ischemia on day 8 does not increase the levels of plasma creatinine when compared with the baseline levels (Fig. 1A). Before the subsequent ischemia on day 8, creatinine levels were indistinguishable from those at baseline in the all groups. The patterns of change in BUN closely paralleled those in creatinine in all experimental groups (Fig. 1B). On day 5 after second ischemic insult, the survival rate is 80% and 100% in the Group II and the Group IV animals, respectively.

Renal ischemia/reperfusion results in disruption of actin cytoskeleton, fragmentation of microvilli and loss of cell polarity (19-22). We evaluated the effect of prior ischemia on post-ischemic histological changes using immunocytochemistry techniques. Sections were stained for phalloidin to identify the actin cytoskeleton (Fig. 2). There is normal phalloidin staining in sham-operated animals (Fig. 2). Ischemia on day 8 in the kidney non-preconditioned results in very severe widespread loss of the brush border actin in the S3 proximal tubular cells in the outer stripe of outer medulla (Fig. 2). In the animals preconditioned, changes in the post-ischemic kidney cytoskeleton actin staining is much less when compared with changes in the non-preconditioned (Fig. 2).

Prior ischemia reduces post-ischemic myeloperoxidase (MPO) activity

To evaluate whether leukocyte infiltration is associated with the increased resistance on the animals preconditioned, extent of tissue leukocyte infiltration was determined by tissue MPO activity which is an index of leukocyte infiltration. Twenty-four hours after ischemia, there is a dramatic increase in MPO activity in the animals non-preconditioned. By contrast, the ischemic preconditioning prevents most of the post-ischemic increase in tissue MPO activity (Fig. 3). There are no changes of MPO activity in the kidneys sham-operated on day 8 (Fig. 3).

Prior ischemia reduces post-ischemic expression of tissue intercellular adhesion molecule-1 (ICAM-1)

Since ICAM-1 can attract and/or activate leukocytes, potentiate small vessel occlusion, and promote further production of inflammatory mediators (16, 23, 24), we evaluated tissue ICAM-1 expression using Western blot and immunocytochemical analysis. Ischemia results in an increased expression of tissue ICAM-1. Six hours after ischemia on day 8, post-ischemic tissue ICAM-1 expression is greater in the kidneys non-preconditioned than in the kidneys pre-conditioned (Fig. 4). Sham-operation does not increase the tissue expression of ICAM-1 (Fig. 4). When the post-ischemic expression of ICAM-1 was immunohistologically evaluated, the expression levels is less in the kidneys preconditioned than in the kidneys non-preconditioned (Fig. 5). After ischemia, ICAM-1 is expressed in the outer stripe of the outer medulla which is most susceptible region to ischemia/reperfusion insult (Fig. 5). The post-ischemic expression of ICAM-1 is greater in the outer medullar than in the cortex. The post-ischemic expression of ICAM-1 is positively correlated with MPO activity. The post-ischemic ICAM-1 expression and MPO activity negatively correlates with the ischemia/reperfusion-induced renal functional and morphological injury.

Discussion

Our studies demonstrate that prior ischemia renders kidney resistant to the remote subsequent ischemia/ reperfusion insult 8 days later. Ischemia results in the increased leukocyte infiltration and ICAM-1 expression. Prior treatment of ischemia mitigates the post-ischemic leukocyte infiltration and ICAM-1 expression. Protective effects of preconditioning are transient and initially last only for a short period of time, i.e. less than 2 hours. A so-called "second window of protection" has been observed in some species, occurring 24 hours after the preconditioning stimulus in neurons and cardiomyocytes (25-27). Recent, we reported in mouse kidneys that the resistance induced by prior ischemia or transient ureteral obstruction was seen up to 15 or 8 days after the initial insults, respectively (6-7). In those studies, we have found that the protection is associated with the reduced post-ischemic activation of stress-activated protein kinase (SAPK) 1/2 or p38 and the increased actin cytoskeleton stability due to the increased heat shock protein-25 expression (6, 7).

Ischemia and reperfusion in the kidney is characterized by marked structural and functional disruption of the proximal tubular epithelial cells in the outer stripe of the outer medulla (21, 22). Ischemia-induced functional damage is directly linked with disruption of actin cytoskeleton, since actin filament support brush-border or membrane solute transporters (19, 21). In these studies, we observed less post-ischemic disruption of the actin cytoskeleton in the proximal tubular cells in the outer stripes of the outer medulla in the kidneys previously subjected to ischemia when compared with the kidneys previously sham-operated. The increased cytoskeleton stability might preserve the polarity of proximal epithelial cells from ischemia/reperfusion injury and then reduce the renal functional disorders

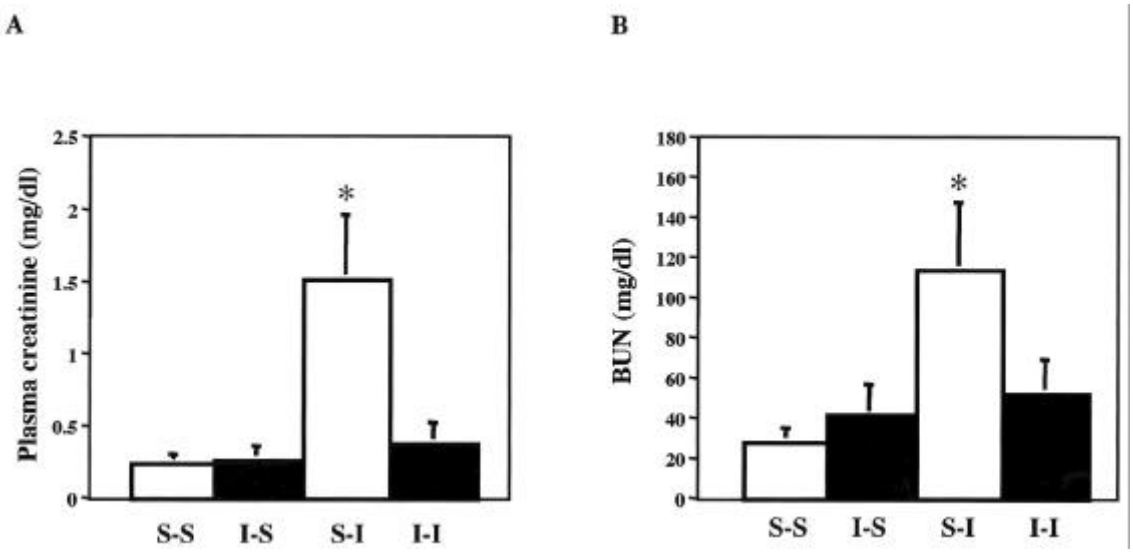

Fig. 1. Effect of prior treatment of ischemia on the levels of (a) plasma creatinine and (b) blood urea nitrogen (BUN) after an ischemia/reperfusion. Animals were subjected to either sham-operation (S) or 30 minutes of bilateral ischemia (I) on day 0. Eighty days after first surgery, animals were subjected to either sham-operation or 30 minutes of bilateral ischemia. Plasma creatinine and BUN levels were measured 24 hours after ischemia. Values are expressed as mean ± S.E.M. *, $p < 0.05$ versus I-I.

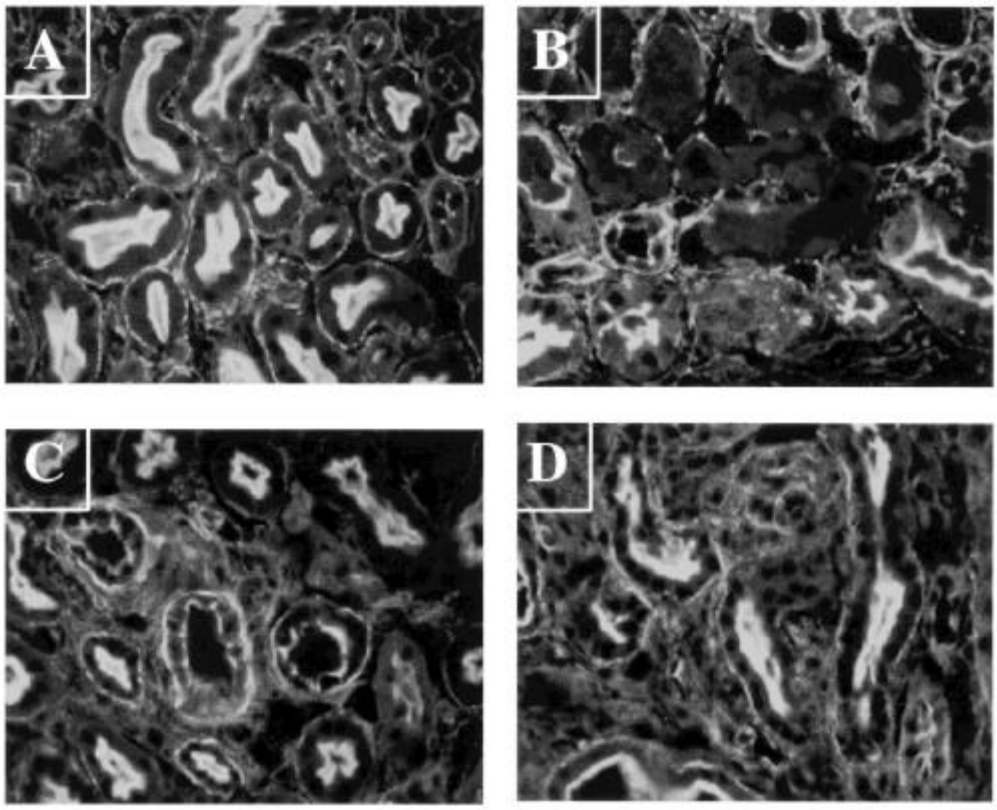

Fig. 2. Immunocytochemical assessment of actin cytoskeleton on kidney sections. Animals were subjected to either sham operation (a and b) or 30 minutes of bilateral ischemia (c and d) on day 0. Eighty days after the first surgery, some animals were exposed to either sham-operation (a and c) or 30 minutes of bilateral ischemia (b and d). The kidneys were harvested 24 hours after the second surgery. The kidney sections were stained with anti-phalloidin antibodies as described in Methods. Sections were taken from outer medulla.

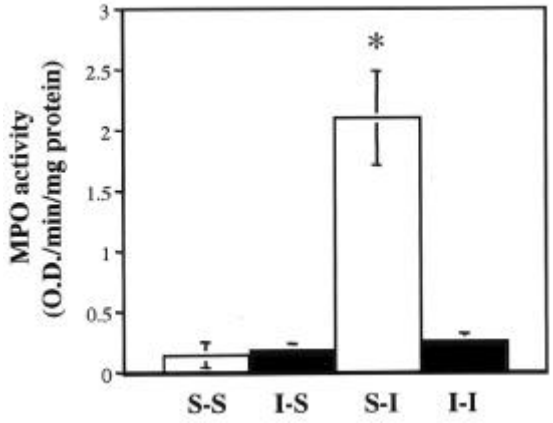

Fig. 3. Effect of prior treatment of ischemia on post-ischemic leukocyte infiltration. Animals were subjected to either sham-operation (S) or 30 minutes of bilateral ischemia (I) on day 0. Eight days after the first surgery, the animals were subjected to either sham-operation or 30 minutes of bilateral ischemia. Twenty-four hours after the second surgery, on day 9, kidneys were harvested and myeloperoxidase (MPO) activity was determined. MPO activity was normalized to protein concentration. Values presented are expressed as mean ± S.E.M in 6 animals. *, $p < 0.01$ vs I-I.

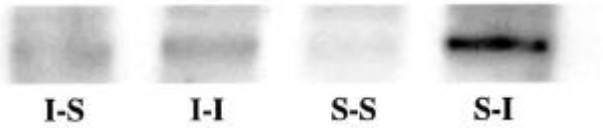

Fig. 4. Effect of prior treatment of ischemia on post-ischemic expression of tissue intercellular adhesion molecule-1 (ICAM-1). On day 0, animals were subjected to either sham surgery (S) or 30 minutes of bilateral ischemia (I). Eight days after the first ischemia, the animals were subjected to either sham-operation or 30 minutes of bilateral ischemia. Six hours after the second surgery, kidneys were harvested and ICAM-1 expression was determined with anti-ICAM-1 antibody on Western blot analysis.

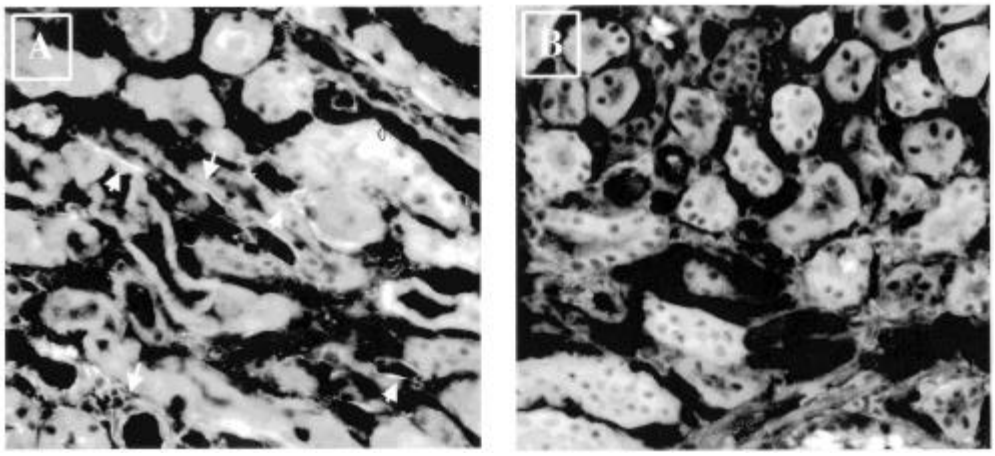

Fig. 5. Post-ischemic expression of intercellular adhesion molecule-1 (ICAM-1) on kidney sections. On day 0, animals were subjected to either sham surgery (A) or 30 minutes of bilateral ischemia (B). Eight days after the first ischemia, the animals were subjected to 30 minutes of bilateral ischemia. Eight hours after the second surgery, kidneys were fixed with 4 % PLP fixative and sections were prepared for immunocytochemical staining. Sections were stained with anti-ICAM-1 antibody as described in Methods. Arrows indicate ICAM-1 expression.

induced by ischemic injury.

Ischemia/reperfusion results in cytokine production which, in turn, can enhance leukocyte-endothelial adhesion interactions in the small vessels of the outer medulla with associated platelet activation, leukocyte adhesion, leukocyte infiltration, and resultant obstruction (17). Following renal ischemia, neutrophils accumulate in the outer stripe of outer medulla. The infiltrated neutrophils harm cell structures or cell function (28), plug the ascending vasa recta in the outer stripe of the outer medulla, and further impair the oxygen supply to the proximal straight tubule, the major site of injury in ischemic renal failure (28-32). Considerable evidence suggests that the inhibition of inflammatory reaction reduce ischemic injury (16, 17). Anti-neutrophil serum treatment

reduces neutrophil count and the neutrophil-depleted animals are protected against ischemic renal failure (16). Furthermore we previously observed that anti-ICAM-1 antibody protected mice against ischemia/reperfusion insult and that mice depleted of ICAM-1 gene are less susceptible to ischemic renal injury (33). In the present studies, we observe the profound reduction of post-ischemic leukocyte- infiltration and expression of ICAM-1 in kidneys previously subjected to ischemia. In recent, we observed that prior ureteral obstruction results in the reduced post-ischemic leukocyte infiltration and congestion in the outer medulla in the kidney (6).

In conclusion, we have demonstrated that prior ischemia renders the kidney resistant to ischemia. The reduced susceptibility in the animals previously subjected to ischemia might be mediated by the mitigated post-ischemic inflammations, leading to ischemia/reperfusion-induced kidney damages. These findings have important implications for understanding of the pathophysiology of ischemia-induced injury and provide a new paradigm for the design of therapies for ischemic diseases.

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