Prevention of Kidney Ischemia/Reperfusion-induced Functional Injury and JNK, p38, and MAPK Kinase Activation by Remote Ischemic Pretreatment*

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MAPK activities, including JNK, p38, and ERK, are markedly enhanced after ischemia in vivo and chemical anoxia in vitro. The relative extent of JNK, p38, or ERK activation has been proposed to determine cell fate after injury. A mouse model was established in which prior exposure to ischemia protected against a second ischemic insult imposed 8 or 15 days later. In contrast to what was observed after 30 min of bilateral ischemia, when a second period of ischemia of 30- or 35-min duration was imposed 8 days later, there was no subsequent increase in plasma creatinine, decrease in glomerular filtration rate, or increase in fractional excretion of sodium. A shorter period of prior ischemia (15 min) was partially protective against subsequent ischemic injury 8 days later. Unilateral ischemia was also protective against a subsequent ischemic insult to the same kidney, revealing that systemic uremia is not necessary for protection. The ischemia-related activation of JNK and p38 and outer medullary vascular congestion were markedly mitigated by prior exposure to ischemia, whereas preconditioning had no effect on post-ischemic activation of ERK1/2. The phosphorylation of MKK7, MKK4, and MKK3/6, upstream activators of JNK and p38, was markedly reduced by ischemic preconditioning, whereas the post-ischemic phosphorylation of MKK1/2, the upstream activator of ERK1/2, was unaffected by preconditioning. Pre- and post-ischemic HSP-25 levels were much higher in the preconditioned kidney. In summary, post-ischemic JNK and p38 (but not ERK1/2) activation was markedly reduced in a model of kidney ischemic preconditioning that was established in the mouse. The reduction in JNK and p38 activation can be accounted for by reduced activation of upstream MAPK kinases. The post-ischemic activation patterns of MAPKs may explain the remarkable protection against ischemic injury observed in this model.

Ischemic injury to brain, heart, and kidney is associated with high morbidity and mortality. Improving the ability of these organs to tolerate ischemic injury would have important implications. Ischemic insults are often recurrent in patients. In the setting of loss of renal blood flow autoregulation that characterizes the post-ischemic kidney (1), it might be expected that the post-ischemic patient would be more susceptible to a second insult. It has been reported in animals, however, that prior acute renal failure induced by toxins can confer resistance to subsequent insults, although this is not a universal finding (2). Zager et al. (3) have focused on early time points after an initial ischemic exposure and have concluded that the rat is not more susceptible to a second ischemic episode when timed at or near the peak of functional deficit after the first. The authors further concluded that “a modicum of protection appears to exist, possibly due to renal failure-induced increments in solute load.” Proximal tubules isolated 24 h (but not 15 min or 4 h) after an ischemic episode are protected against hypoxia, reactive oxygen species, or calcium ionophore in vitro (4, 5). The lack of protection at 4 h and the induction of protection by inducing azotemia in vivo or adding urine to the tubules in vitro led the authors to conclude that the protection is due to the uremic environment. Subsequently protection was found in tubules obtained from obstructed kidneys even when the tubules had not been exposed to a uremic environment (6). In a recent study (7), four cycles of 8 min (but not 4 or 6 min) of ischemia, separated by 5 min of reperfusion, conferred protection against a subsequent 45-min ischemic exposure immediately after the four cycles. In another recent study, four cycles of 4 min of ischemia, separated by 11 min of reperfusion, followed 5 min later by 45 min of ischemia, resulted in fewer dead renal cells, but no difference in creatinine at 6 h post-ischemia with this preconditioning protocol (8). It had previously been shown that there were no morphological differences with this preconditioning protocol if the time delay between the cycles and the prolonged ischemia was 30 min (9). Thus, controversy remains as to the conditions under which preconditioning occurs in the kidney in response to prior ischemia. In addition, the reported experiments are limited to the study of short intervals of time between the preconditioning protocol and the tested period of subsequent ischemia.

One approach to the design of therapies to protect the kidney against ischemic injury is to establish a model in which endogenous mechanisms result in protection and then identify those processes. A model in mice would be particularly useful given the plethora of transgenic models that exist, which would facilitate exploration of the role of a particular protein in the protection. Furthermore, we wanted to establish a model in which the acute cellular and molecular response to the initial event had subsided, reducing the “background” genetic response so that it would be more possible to identify an endog-

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enous protective factor or factors.

Our experiments demonstrate that 30 min of bilateral renal ischemia, resulting in significant increases in blood urea nitrogen and creatinine, leads to protection of the mouse kidney against a subsequent ischemic insult 8 or 15 days later, even when the second ischemic period is extended to 35 min. Graded levels of time of initial ischemia resulted in graded levels of protection 8 days later. This protection is unrelated to systemic effects of transient uremia since unilateral ischemia is also associated with protection under conditions in which there is very little increase in systemic blood urea nitrogen or creatinine. Preconditioning results in prevention of medullary congestion. With varying times of initial ischemia, the protection afforded 8 days later correlates with the level of sustained elevations in HSP-25\(^1\) (HSP-27 in rat) protein levels prior to the second ischemic period, but not superoxide dismutase or HSP-72 levels.

The MAPKs have been implicated in post-ischemia/reperfusion cell survival, necrosis, and apoptosis (10–12). MAPKs mediate the response of cells to a wide variety of physiological and stress-related stimuli, including ultraviolet light, heat shock, ischemia, oxygen free radicals, and hyperosmolality. It has been proposed that activation of JNK and p38 kinases contributes to cell death, whereas activation of ERK1/2 contributes to protection against cell injury in multiple organs (11, 13). We examined whether the effect of ischemic preconditioning to protect the kidney is associated with corresponding changes in stress kinases and ERKs as well as their upstream activating kinases, which might account for the functional protection observed. Post-ischemic activation of JNK and p38 is markedly mitigated in the preconditioned kidneys, as is the post-ischemic activation of the MAPK kinases MKK7, MKK4, and MKK3/6, upstream activators of JNK and p38. By contrast, the post-ischemic activation of MKK3/4, the MAPK kinases responsible for activating ERK1/2, is unaltered by preconditioning.

**EXPERIMENTAL PROCEDURES**

**Animal Preparation**—All experiments were performed with male BALB/c mice (Charles River Laboratories) weighing 20–25 g. Mice were allowed free access to water and standard mice chow. Blood was drawn, and base-line levels of serum creatinine and blood urea nitrogen were determined 2 days before surgery. Animals were anesthetized with pentobarbital sodium (50 mg/kg intraperitoneally) and administered 1 ml of 0.9% NaCl (37 °C) on the day of surgery (day 0). Body temperature was maintained at 36.0–37.5 °C. Animals were divided into 13 (1–XIII) groups (Table I). Kidneys were exposed through flank incisions. Mice in Groups II–IV, VI, and VII were subjected to bilateral renal ischemia by clamping both renal pedicles with nontraumatic microaneurysm clamps (Roboz Surgical Instrument Co., Inc.). Animals in Groups I, V, and VIII underwent sham surgery. The incisions were temporarily closed during ischemia or sham surgery. After 5 (Group II), 15 (Group III), or 30 (Groups IV, VI, and VII) min, the clamps were removed, and reperfusion of the kidneys was visually confirmed. Animals were exposed to 30 (Groups I–IV) or 35 (Groups V and VI) min of bilateral ischemia on day 8 or 30 min of ischemia on day 15 (Groups VII and VIII).

Mice in Groups IX–XIII underwent unilateral ischemia for 30 min. In Group IX, the contralateral kidney was removed on day 2, whereas in Group X, the contralateral kidney was removed on day 8, at the time of the second ischemia. In Group XI, the left kidney was made ischemic on day 0; the contralateral kidney was removed on day 8; and the left kidney was made ischemic again on day 15. In Group XII, the left kidney was made ischemic for 30 min on day 0. On day 8, that kidney was removed, and the right kidney was made ischemic on day 15. In Group XIII, ischemia to one kidney on day 0 was followed by ischemia to the contralateral kidney on day 8, and bilateral ischemia was imposed on day 15.

Kidneys of experimental groups were harvested on day 1, 2, or 8 after the first surgery or 24 or 48 h after the second ischemic period. Kidneys were snap-frozen in liquid nitrogen and subsequently used for Western analysis or were rinsed in phosphate-buffered saline and fixed in 4% paraformaldehyde for histological analysis.

**Renal Functional Parameters**—Seventy microliters of blood were taken from the retrobulbar vein plexus at the times indicated in the figures. Plasma and urine sodium, creatinine, and blood urea nitrogen concentrations were measured using a flame photometer, a Beckman Creatinine Analyzer II, or a spectrophotometer (blood urea nitrogen). To determine glomerular filtration rate and fractional excretion of sodium, urine was collected for 24 h.

**Western Blot Analysis**—Proteins were extracted from kidneys as previously described (10). Protein samples were separated on either a 10 or 12% SDS-polyacrylamide gel and then transferred to an Immobilon membrane. Membranes were incubated with antibodies against active phospho-JNK(Thr183/Tyr185), active phospho-p38(Thr180/Tyr192), active phospho-ERK1/2(Thr202/Tyr204), phospho-SEK1/MKK4, phospho-MEK1/2, MEK1/2, phospho-MKK3/6, and MKK3 (Cell Signaling); JNK1, ERK1/2, and p38 (Santa Cruz Biotechnology); phospho-MKK7 (provided by A. Nelsbach, Cell Signaling); HSP-27 (Upstate Biotechnology, Inc.); and superoxide dismutase (Chemicon International, Inc.). Secondary antibodies conjugated with horseradish peroxidase (Santa Cruz Biotechnology) were detected by the ECL system (Amersham Pharmacia Biotech).

**Immunoprecipitation of JNK and Immune Complex Kinase Assays**—Supernatants from mouse kidney lysates were matched for protein concentration prior to immunoprecipitation with a polyclonal anti-JNK antibody (provided by A. Nelsbach, Cell Signaling) or a spectrophotometer (blood urea nitrogen). Secondary antibodies conjugated with horseradish peroxidase (Santa Cruz Biotechnology) were detected by the ECL system (Amersham Pharmacia Biotech).
S-transferase-c-Jun-(1–135) were cut out of the gel. Radioactivity was measured by liquid scintillation counting.

**Histology**—Kidneys were perfused via the left ventricle with phosphate-buffered saline at 37 °C and then with paraformaldehyde lysine periodate (14) for 10 min. In some cases, the tissue was embedded in paraffin, sectioned to 6-μm thickness, and stained with hematoxylin and eosin.

**Statistics**—All results are expressed as means ± S.E. A *p* value <0.05 was taken as statistically significant. Each group consisted of 4–10 animals as indicated in Table I.

## RESULTS

**Effects of Prior Ischemia on Renal Function after Subsequent Ischemia/Reperfusion**—Animals were exposed to 0 (Group I) or 5, 15, or 30 min (Groups II–IV) of bilateral renal ischemia (Fig. 1A). Plasma levels of creatinine increased 5–8-fold over baseline levels 24 h post-ischemia only when the ischemic period was 30 min. By day 5 after ischemia, creatinine levels were indistinguishable from those at base line in all groups. On day 8 after the initial ischemia or sham procedure, a subsequent 30 min of bilateral ischemia was induced. The increase in creatinine measured 24 h later was inversely correlated with the length of time of the prior ischemia. There was no significant increase in serum creatinine at 24 and 48 h after the second ischemic period in animals that were previously exposed to 30 min of ischemia. The patterns of change in blood urea nitrogen after the first and second ischemic periods closely paralleled those in creatinine in these and all subsequent experiments (Fig. 1B). The glomerular filtration rate was markedly decreased during the first day after 30 min of ischemia, but returned to normal within 7 days of reperfusion (Fig. 1C). Likewise, fractional excretion of sodium was markedly increased during the first day of reperfusion, but returned to normal levels by 7 days of reperfusion (Fig. 1D). A subsequent second 30-min ischemic period resulted in no decrease in glomerular filtration rate or increase in fractional excretion of sodium.

Necrosis was found in kidneys from Group IV 48 h after 30 min of bilateral ischemia. Neutrophils were found in the outer medulla. The kidneys of sham-operated animals were normal. On day 8, the repair of injured tubules was almost complete. Regenerated tubules were seen, and some tubules were dilated and cystic. When kidneys were examined 48 h after the second ischemia, the “preconditioned” kidneys (Group IV) had no significant outer medullary congestion, whereas there was very significant congestion in the outer medulla of sham-pretreated animals examined after their first exposure to ischemia (Group I) (Fig. 2A). Microscopic examination revealed much less necrosis of proximal tubule cells, obstruction, and red cell trapping in the outer medulla of ischemia-pretreated preconditioned animals (Group IV) compared with Group I controls (Fig. 2, B and C).

When the first ischemic period was 30 min and the second was extended to 35 min (Group VI), serum creatinine did not increase after the initiation of reperfusion (Fig. 3). When the length of time between bilateral ischemic exposures was lengthened to 15 days (Group VII), serum creatinine increased by 24 h after the second ischemic insult (Fig. 4); however, the increase was significantly lower than that observed in animals that had been previously sham-operated on day 0 (Group VIII).

**Unilateral Renal Ischemia Followed 8 Days Later by Ischemia/Reperfusion**—To evaluate whether ischemia itself was protective independent of systemic effects of uremia, animals were exposed to sham surgery or unilateral left kidney ischemia (Groups I, IX, and X) for 30 min on day 0. We considered that the presence of a normal contralateral kidney might influence mechanisms contributing to protection against a subsequent ischemic exposure to a kidney rendered unilaterally

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**FIG. 1.** Effect of prior ischemia of varying durations on serum creatinine (A), blood urea nitrogen (BUN; B), glomerular filtration rate (GFR; creatinine clearance) (C), and fractional excretion of sodium (FE\textsubscript{Na}; D) after a second period of ischemia. Animals were subjected to either sham surgery (S; Group I) or 5, 15, or 30 min of ischemia (I; Groups II–IV). Eight days after the first surgery, animals were subjected to bilateral ischemia for 30 min. Values are expressed as means ± S.E. Arrows indicate the day of ischemia or sham surgery. *p* < 0.001 (*) and *p* < 0.05 (#) versus sham ischemia. BW, body weight.
After 35 min of a second period of ischemia on day 8.

On day 0, after 30 min of a second period of ischemia on day 15.



FIG. 2. A, hemisected kidney perfusion-fixed after sham surgery (Sham) or ischemia (Isch.) (day 0), ischemia (day 8), and 48 h of reperfusion. B and C, light microscopy of kidneys treated as described for A. There was significant greater necrosis of tubule cells, tubular obstruction, and vascular congestion in the outer medulla in Group I animals (B) compared with Group IV animals (C). Bar = 100 μm.

FIG. 3. Effect of prior ischemia for 30 min on serum creatinine after 35 min of a second period of ischemia on day 8. On day 0, animals were subjected to either sham surgery (S; Group VI) or 30 min of ischemia (I; Group VII). Eight days after the first surgery, animals were subjected to bilateral ischemia for 35 min. Arrows indicate the day of ischemia or sham surgery. *, p < 0.001 versus sham ischemia.

FIG. 4. Effect of prior ischemia for 30 min on serum creatinine after 30 min of a second period of ischemia on day 15. On day 0, animals were subjected to either surgery sham (S; Group VIII) or 30 min of ischemia (I; Group VII). Fifteen days after the first surgery, animals were subjected to bilateral ischemia for 30 min. Arrows indicate the day of ischemia or sham surgery. p < 0.001 (*) and p < 0.05 (#) versus sham ischemia.

unilateral ischemia protected kidney against subsequent ischemia even in the absence of an increase in serum creatinine (Fig. 5). If the contralateral kidney was left in for 8 days, however, the protection was less than was seen when the contralateral kidney was removed at 2 days post-ischemia.

In Group XIII, the left kidney was rendered ischemic on day 0; the right kidney was made ischemic for 30 min on day 8; and both kidneys were made ischemic on day 15. There was protection against ischemic injury under these conditions, with no increase in serum creatinine 24 h after the bilateral ischemia (Fig. 6). To evaluate whether unilateral ischemia confers protection on the contralateral kidney, in Group XII, the left kidney was made ischemic for 30 min on day 0 and subsequently removed on day 8, and the right kidney was made ischemic for 30 min on day 15. Twenty-four hours later, the mean serum creatinine was markedly elevated (Fig. 6), indicating that unilateral ischemia did not confer protection on the contralateral kidney.

Effect of Ischemic Preconditioning on the Levels of HSPs and Superoxide Dismutase—We evaluated whether HSPs or superoxide dismutase protein levels correlate with the development of resistance to subsequent ischemia. The levels of HSP-25 at 8 days post-ischemia increased with time of ischemia (Fig. 7A), correlating well with the extent of protection against functional deficits after the second ischemic period (Fig. 1). After the second ischemic period, HSP-25 levels markedly increased to higher levels than in the preconditioned kidneys (Fig. 7B), whereas HSP-72 levels were not different whether the first procedure was ischemia or sham surgery (Fig. 7A). The tissue protein levels of superoxide dismutase (15-kDa subunit) were not markedly changed at 8 days post-ischemia (data not shown).

Effect of Ischemic Preconditioning on Activity of MAPKs and MAPK Kinases—The JNK family of MAPKs (also known as SAPKs) is markedly activated as early as 5 min after ischemia/reperfusion, peaks at 20 min, but remains at relatively high levels up to 2 h post-ischemia (10). In these studies, we have found that JNK activity remained above control levels at 48 h of reperfusion (Fig. 8A). In animals previously exposed to ischemia, subsequent ischemia on day 8 or 15 resulted in much less activation of JNKs than was seen in post-ischemic kidneys not previously exposed to ischemia (Fig. 8A). When activation was determined by immunoblotting with the anti-phospho-JNK antibody, a similar pattern was seen, with marked reduction of the ischemia-induced increase in phospho-JNK at 0.5 and 1.5 h post-ischemia in the animals exposed to ischemia 8
days previously (Fig. 8A, lower panel). Likewise, post-ischemic p38 activation was markedly reduced in kidneys previously exposed to ischemia (Fig. 8B). ERK1/2 activation persisted 8 days after the initial ischemic exposure; but in contrast to JNK and p38, there was no effect of prior ischemia on post-ischemic ERK phosphorylation on day 8. Kidneys were harvested at the indicated times after the ischemic period. Densities of Western blot bands were quantified by the NIH Image program. Data are presented as the mean from three separate experiments.

To evaluate whether activation of JNK, p38, and ERK1/2 is potentially explained by changes in activation patterns of upstream regulators of these kinases, we compared the response to ischemia of MKK7 (which activates JNK), MKK4 (which activates JNK and possibly p38), MKK3/6 (which activate p38), and MEK1/2 (which activate ERK1/2) in kidneys previously exposed to ischemia or sham surgery (Fig. 9). The post-ischemic increase in phosphorylation of MKK7, MKK4, and MKK3/6 was much less in the preconditioned kidney than in the non-preconditioned kidney. By contrast, post-ischemic phosphorylation of MEK1/2 was not decreased by preconditioning. Whereas phosphorylation of MKK7 peaked at 1.5 h after ischemia, phosphorylation of MKK4, MKK3/6, and MEK1/2 peaked at 0.5 h.
Protection is not dependent on the presence of a uremic systemic environment since 15 min of initial ischemia resulted in protection against subsequent ischemia without causing an increase in blood urea nitrogen. A local effect within the kidney is likely responsible for protection against subsequent ischemia since protection was observed in the same kidney that sustained unilateral ischemia, but not in the contralateral kidney. Our finding that the protection was greater when the contralateral kidney was removed on day 2 compared with day 8 is compatible with prior observations of the adverse effects of the presence of the contralateral kidney on the functional recovery of a unilaterally ischemic kidney (15).

In the heart, although preconditioning is a very effective way to reduce post-ischemic infarct size, the protective effects of preconditioning are transient and initially last only for a short period of time, i.e. <2 h. A so-called “second window of protection” has been observed in some species (19), occurring 24 h after the preconditioning stimulus in neurons and cardiomyocytes. In our study, the protection in the mouse kidney after ischemia was seen up to 15 days after the initial ischemic period, when most, but not all, of the metabolic and stress responses associated with ischemia have been resolved.

The degree of protection against the second ischemic insult after a first ischemic period of varying time duration correlated positively with levels of heat shock protein expression at 8 days post-ischemia. HSPs may decrease production of cytokines (20), reducing leukocyte-endothelial interactions and mitigating congestion in the outer medulla, resulting in less hypoxic injury to the outer medullary tubules. It has been suggested that HSP-25 protects against oxidative or heat stress by stabilizing the actin cytoskeleton (21). The actin cytoskeleton is markedly altered in the proximal tubule after ischemia (22, 23). Another important role of HSP-25 is that of a molecular chaperone efficiently trapping unfolding proteins in a folding-competent state, allowing refolding after restoration of physiological conditions post-ischemia (24). HSP-25 can also increase cellular levels of glutathione (25), which can protect the cell against oxidative stress, reduce stress kinase activation (13), and inhibit apoptosis (26). HSP-25 levels increase in the cortical and outer medullary proximal tubules of rat kidneys post-ischemia (27). By contrast to HSP levels, changes in manganese-superoxide dismutase protein levels, implicated in the delayed phase of preconditioning in the dog heart (28), did not correlate with protection of the kidney in our experiments.

Our demonstration of increases in JNK, p38, and ERK1/2 activation with ischemia is consistent with previous published results from our laboratory (10) and others (29) in the kidney and other organs. In the heart, some have argued that activation of p38 is important for preconditioning (30), whereas others have argued that activation is detrimental and that a reduced level of activation is important for preconditioning (31).

It was previously not known how the upstream kinases responsible for activation of the MAPKs are affected by kidney ischemia. Our data indicate that ischemia/reperfusion results in the activation of MKK3/6 and MKK4. Both are activators of p38, although the physiological relevance of MKK4 as an activator of p38 is unclear. This ischemia-induced activation is reduced in kidneys previously exposed to ischemia in a pattern that parallels that of p38 activation. JNK is activated by dual phosphorylation on threonine and tyrosine by MKK4 and MKK7 (32). Ischemia/reperfusion results in MKK4 and MKK7 activation. This post-ischemic activation is reduced in kidneys previously exposed to ischemia in a pattern that parallels that of p38 and JNK activation. Interestingly, MKK7 activation peaks at 1.5 h after ischemia and persists longer than JNK.
activation. This suggests that post-ischemic JNK activation may be more dependent upon MKK4 than MKK7 activation. In contrast to the upstream activators of the stress kinases, post-ischemic MEK1/2 activation is not reduced in the preconditioned kidney. The increase in MEK1/2 with a resultant increase in ERK1/2 activation post-ischemia/reperfusion in the setting of reduced stress kinase activation may explain the protection seen with preconditioning in the kidney. It has been proposed in neurons (11) and proximal tubule cells (33) that the relative extent of JNK, p38, and ERK activation may determine cell fate, with JNK activation associated with cell death and ERK activity protective. JNK has recently been implicated in the mitochondrial death pathway (34), and activation of the JNK cascade has been reported to be important for cardiomyocyte death in response to simulated ischemia (35).

The functional protection we observed is associated with a marked reduction in outer medullary congestion post-ischemia, which may be related to decreased cytokine-induced leukocyte-endothelial interactions associated with the decrease in activation of JNK/SAPK and p38. JNK and p38 activity enhances the expression of adhesion molecules (36) and cytokine production of JNK cascade has been reported to be important for cardiomyocyte death in response to simulated ischemia (35).

In summary, we have demonstrated that the mouse kidney is profoundly protected against ischemia/reperfusion injury up to 15 days after an initial ischemic insult. This observation points to powerful endogenous mechanisms that can be evoked by the kidney to protect itself against ischemic injury. This protection is associated with prevention of outer medullary vascular congestion and mitigation of the increase normally seen in JNK and p38 activity, with no effect on ERK1/2 activation. The effects of remote ischemic pre-exposure on MAPK kinase activation can explain the changes observed in MAPK activation patterns. Since protection is present long after many of the initial consequences of the ischemia/reperfusion have subsided, it is likely that a genomic or proteomic approach to mechanisms, involving identification of “protective” proteins that are up-regulated or “detrimental” proteins that are down-regulated, will be tractable. This will then hopefully lead to therapies that will be effective in preventing and/or treating ischemic acute renal failure.

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