

KIDNEY ISCHEMIC PRECONDITIONING

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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 (8). Ischemic insults are often recurrent in patients. A significant amount of data now exists in a number of organs to suggest that there may be intrinsic mechanisms brought to bear by organs exposed to a toxic or ischemic insult which protect them against a subsequent exposure to ischemia (2).

Our laboratory created a mouse model in which prior exposure to ischemia protects against a second ischemic insult imposed 8 or 15 days later (5). In contrast to the increase in creatinine, decrease in glomerular filtration rate (GFR) and increase in fractional excretion of sodium (FE_{Na}) that normally results from 30 minutes of bilateral ischemia, when a second period of ischemia of 30 or 35 min duration is imposed 8 days later, there are no significant changes in these functional parameters. A shorter period of prior ischemia (15 min) is partially protective against subsequent ischemic injury 8 days later. Unilateral ischemia is also protective against a subsequent ischemic insult to that kidney revealing that systemic uremia is not necessary for protection. Protection against ischemic kidney injury is also afforded by 24 h of ureteral obstruction (UO) applied 6 or 8 days prior to the ischemia (6).

What are the mechanisms that account for kidney ischemic preconditioning ?

There are a number of possible explanations for ischemic preconditioning. We have reported that the ischemia-related activation of JNK and p38 and outer medullary vascular congestion are markedly mitigated by prior exposure to ischemia whereas preconditioning has no effect on post-ischemic activation of ERK1/2. Prior ureteral obstruction also results in reduced post-ischemic outer medullary congestion and leukocyte infiltration. The dynamic balance between ERK and JNK-p38 pathways has been proposed to determine whether neurons (9) and kidney cells (3) survive or undergo apoptosis. The phosphorylation of MKK7, MKK4 and MKK3/6, upstream activators of JNK and p38, are markedly reduced by ischemic preconditioning, whereas the post-ischemic phosphorylation of MEK1/2, the upstream activator of ERK1/2, is unaffected by preconditioning. Prior ureteral obstruction results in reduced post-ischemic phosphorylation of c-jun N-terminal stress-activated protein kinase1/2 (JNK1/2), and p38, mitogen-activated protein kinase (MAPK) kinase 4 (MKK4), and MKK3/6. Very few cells are PCNA positive after obstruction indicating that subsequent protection against ischemia is not related to proliferation with increased number of newly formed daughter cells more resistant to injury.

Post-ischemic HSP-25 levels are much higher in the ischemia-preconditioned kidney. It is possible that the small molecular mass HSP-25 may stabilize the actin cytoskeleton post-ischemia (1) and/or contribute to the alteration in expression of these kinases.

Obstruction also increases the expression of heat shock protein (HSP)-25 which persists for 6 or 8 days. Increased HSP-25 expression is localized to the proximal tubule cells in the outer stripe of the outer medulla post-obstruction. In LLC-PK₁ renal epithelial cells adenoviral-expressed human HSP-27, a member of the HSP-25 family, confers resistance to chemical anoxia and oxidative stress. Increased HSP-27 expression in LLC-PK₁ cells results in reduced H₂O₂-induced phosphorylation of JNK1/2, p38 and ERK1/2.

The fact that “preconditioned” kidneys had no significant outer medullary congestion suggests the possibility that the kidneys are protected because of a decrease in leukocyte-endothelial interactions with less vascular obstruction. This could be due to a number of factors. This could be due to decreased cytokine or chemokine production in the preconditioned kidney. JNK and p38 activation enhances the expression of adhesion molecules and cytokine production which, in turn, can enhance leukocyte-endothelial adhesion interactions in the small vessels of the outer medulla with associated platelet activation and resultant obstruction, leading to S3 segment injury. The dramatic reduction in post-ischemic outer medullary congestion in the kidney previously exposed to ischemia argues for an important effect of preconditioning to prevent small vessel leukocyte- and perhaps platelet-endothelial interactions. In the heart some have argued that activation of p38 is important for preconditioning while others have argued that activation is detrimental and a reduced level of activation is important for preconditioning.

We characterized the time characteristics of the protective effect of ischemic preconditioning, whether the protective mechanisms differ according to the strength of ischemic preconditioning, and whether ischemic preconditioning in the kidney is dependent upon NOS expression (4). Our results indicate that prior ischemic preconditioning protects the kidney from ischemia/reperfusion insults up to 12 weeks later with the degree of protection decreased as length of time between ischemic period increases. Thirty min of ischemic preconditioning results in sustained increases in iNOS expression and sustained damage to the kidney as reflected by α -smooth muscle actin (SMA) accumulation. Pharmacological inhibition of NO synthesis or genetic deletion of the iNOS gene, but not the eNOS gene, increases mouse kidney susceptibility and mitigates the protection afforded by 30 min but not 15 min of ischemic preconditioning. Fifteen min of ischemia does not lead to increases in iNOS or eNOS. Thus increases of iNOS expression account for an important component of long-term ischemic preconditioning in the kidney when the initial ischemia results in persistent tissue injury. We found persistent long-term renal interstitial changes after ischemia in the mouse kidney and implicate these changes in long-term protection against subsequent ischemia.

Does Preconditioning Occur on Humans?

At the present time the literature supports the view that preconditioning reduces subsequent ischemic injury in the human heart, liver, lung, brain and skeletal muscle (7). In the kidney at first glance the clinician may reject the concept since he/she is well aware of many situations where mild tubular injury progresses to acute tubular necrosis and acute renal failure when the patient’s condition deteriorates. It is possible, however, that under these conditions the natural defense mechanisms are overcome. What about all

the other patients who have had a mild subclinical insult to their kidney and who never develop acute renal failure? Perhaps this is a clinical reflection of preconditioning.

Conclusion

In conclusion the protection afforded the experimental animal kidney against acute renal failure by preconditioning is profound and reproducible. Since acute renal failure associated with ischemia continues to be associated with a very high mortality rate in man, it is important to understand how the kidney uses endogenous processes to protect itself. We should take our guidance from the kidney itself and try to understand a process that it has evolved to protect itself. With this understanding, it might be possible to mimic these processes using exogenous influences and hence present and/or alter the cause of a disease which continues to be associated with very high mortality rates.

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