

Inhibition of the JNK apoptotic signalling pathway as a protective mechanism against renal injury after ischemia

Tejas Patel, Qing Ma, Prasad Devarajan

Division of Pediatric Nephrology, Cincinnati Children's Hospital Medical Center

Background: Renal ischemia-reperfusion injury (IRI) has been found as the major cause of acute renal failure, of which is partly due to apoptosis resulting from ATP depletion. The purpose of this study was to determine if inhibition of the Daxx/ASK1/JNK signal transduction pathway would prevent apoptotic activation, and therefore renal injury after ischemia. **Methods:** Mice (control, untreated ischemic, and JNK inhibitor pretreated) were clamped bilaterally on the renal artery for 30 minutes and kidneys/blood were harvested 24 hours after reperfusion. Additionally, two separate groups of mice were pretreated with a JNK agonist with and without 30 minute ischemia and were sacrificed at 24 hours. Paraffin embedded sections were stained with H&E (histologic evaluation) and TUNEL Assay (apoptotic evaluation). Serum creatinine was determined to assess kidney function. **Results:** JNK inhibition markedly decreased apoptosis which was shown through kidney sections with TUNEL staining. H&E slides of tissue treated with the inhibitor also resulted in significant preservation of histological structure. However, serum creatinine values only showed moderate improvement of kidney function after inhibitor pretreatment. Injection of higher doses of JNK inhibitor revealed no significant differences. Furthermore, JNK agonist samples demonstrated only a slight increase in apoptosis without IRI. Agonist models with clamping revealed aggravation of IRI. **Conclusion:** Though these trials resulted in marked structural protection, these results suggest pretreatment with JNK inhibitor results in only partial improvement in kidney function. Because there is still some apoptosis, despite increasing JNK inhibition dosage, along with the ineffectiveness of the JNK agonist, other apoptotic pathways may also be involved. Furthermore, the substantial amelioration of apoptosis with only a partial decrease of serum creatinine may illustrate that apoptosis is only partly responsible for acute renal failure following IRI.