Pharmacological inhibition of IκB kinase reduces the multiple organ dysfunction associated with hemorrhagic shock in the rat

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Multiple organ failure (MOF) induced by shock is associated with a high mortality, being therapies aiming organ protection urgently needed [1]. The nuclear factor kappa B (NF-κB) activation is widely implicated in MOF. Activation of NF-κB is initiated by the signal-induced ubiquitylation and subsequent degradation of inhibitors of kappa B (IκBs) primarily via activation of the IκB kinase (IKK). There is now growing evidence that inhibition of the activation of NF-κB may reduce the organ injury and dysfunction in septic and hemorrhagic shock (HS) [2]. We have recently demonstrated that the inhibition of IKK complex by IKK16 and the consequent prevention of the activation of NF-κB reduce the cardiac dysfunction, liver injury and renal dysfunction caused by sepsis [3]. However, so far, the effects of the specific inhibition of the IKK pathway in HS have yet to be investigated. Thus, the aim of the present work was to study the effects of a direct inhibitor of IκB kinase (IKK), IKK16, on the MOF associated with HS. Male Wistar rats (n=39) were subjected to HS and were resuscitated with the shed blood. Rats were treated with IKK16 (1 mg/mL/kg) or vehicle (10% DMSO) at the resuscitation. Four hours later, blood and organs were harvested for organ injury assessment and signalling events involved on the activation of NF-κB. Additionally, survival following serum deprivation was assessed in a proximal tubular epithelial cell line from human kidney, HK-2 cells, treated with the inhibitor of IKK in the concentration range 10 nM - 100 nM.

When compared to sham-operated rats, HS-rats treated with vehicle showed a significant increase in the serum levels of creatinine, AST and ALT as well as amylase and lipase, indicating the development of renal dysfunction, liver and pancreatic injury, respectively. Besides, rats treated with vehicle also had elevated plasma concentrations of CK and lactate, indicating the development of skeletal muscular injury and global tissue hypoxia, respectively. Markers of neutrophils and macrophages accumulation were drastically increased in the rat lung, kidney and liver following HS. Treatment of HS-rats with IKK16 significantly attenuated the renal dysfunction, liver injury, pancreatic injury and neutrophil/macrophage accumulation but not the skeletal muscular injury associated with HS. Kidney and liver tissue from HS rats revealed increases in phosphorylation of IKKαβ, IκB, nuclear translocation of NF-κB and expression of iNOS. IKK16 treatment upon resuscitation attenuated NF-κB activation and this effect was associated with a robust reduction of the HS-induced increase in serum concentrations of cytokines (TNF-α, IL-6 and IL-10). Interestingly, we discovered that the Akt survival pathways was significantly activated in tissue biopsies of kidney and liver obtained from HS-rats that had been treated with IKK16.

We also documented that IKK16 exhibited cytoprotective effects in human kidney cells.

In conclusion, the inhibitor of IKK complex attenuated the MOF associated with HS. This effect may be due to the inhibition of NF-κB pathway, leading to prevention of excessive inflammation, and the simultaneous activation of the survival kinase Akt. Thus, the inhibition of IKK complex might be an effective strategy for the prevention of MOF associated with HS.

References

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