Preservation of Hypoxia-inducible Factor-1 Induced by ERK Phosphorylation Is Involved in Hypothermic Protection of Renal Ischemia-Reperfusion Injury

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OBJECTIVES

Although hypothermia attenuates renal injury induced by ischemia-reperfusion (IR), precise molecular pathways have not been known yet. Our previous study showed ERK phosphrylation plays an important role in hypothermic protection in renal IR injury. Hypoxia-inducible factor-1(HIF-1) has been known as one of the potent protective proteins in IR injury. We evaluated the role of HIF-1 and interaction with ERK phosphorylation in hypothermic protection of renal IR injury.

METHODS

C57Bl/6 mice were divided into four groups; sham operated mice, cold IR mice(30°C), warm IR mice(37°C) and PD98059(MAP kinase kinase inhibitor) treated cold IR mice(IR injury; reperfusion 27 minutes after clamping of both renal artery and vein). Kidneys were harvested at 10min and 27min after both renal artery ischemia and 24hr after IR injury. Renal HIF-1, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha(PGC 1-alpha), AMP-activated protein kinase(AMPK), and 8-hydroxydeoxyguanosine(8-OHdG) were evaluated by western blot and immuohistochemical stain. BUN and serum creatinine(s-Cr) were measured 24 hrs after IR injury. TUNEL staining and light microscopic examination of kidneys was performed to evaluate the magnitude of renal injury.

RESULTS

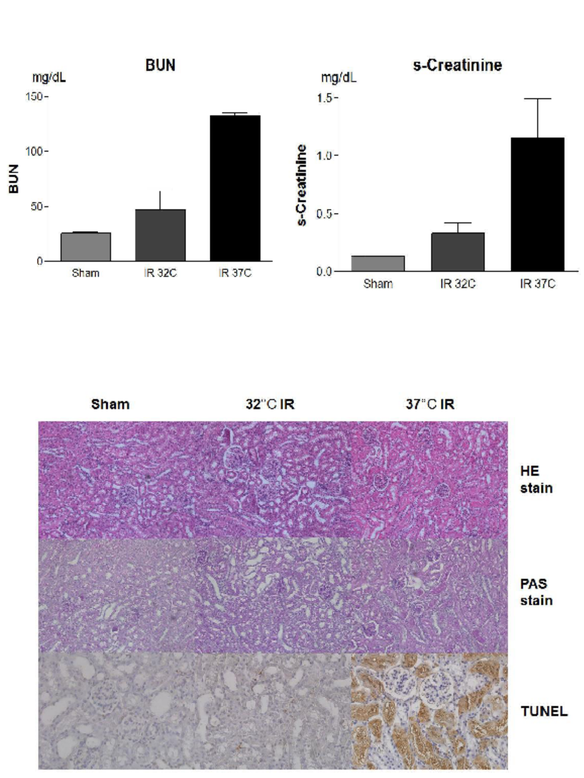

Figure 1. Serum level of BUN and s-Cr in 32°C IR mice was significantly lower than that of 37°C IR mice. Tubular cell detachment, necrosis and TUNEL positive cells in kidneys of cold IR mice(32°C) were significantly higher than those of untreated warm IR mice(37°C)

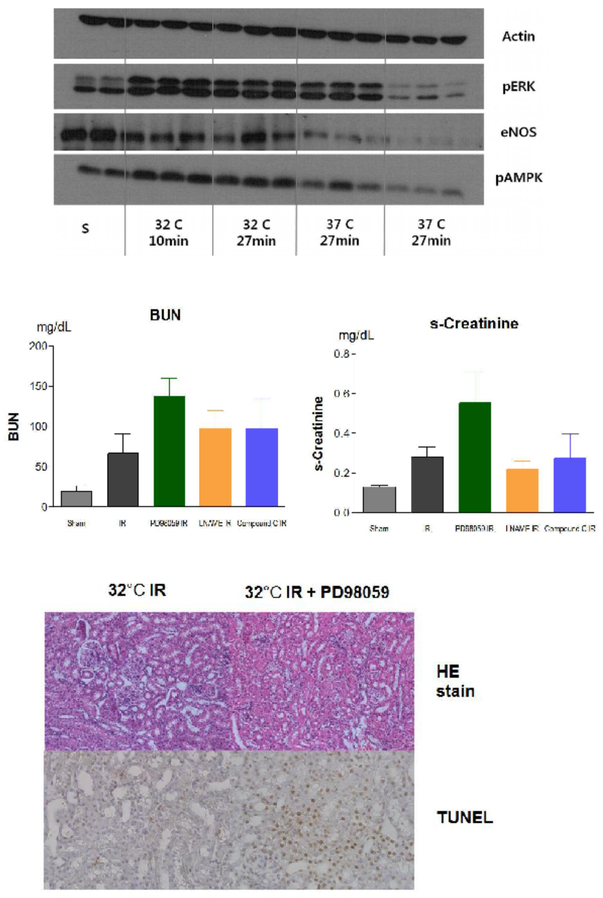

Figure 2. pERK, eNOS, pAMPK expression were increased in cold IR mice at ischemic kidney(10min and 27min after both renal artery clamping). The serum level of BUN and creatinine in PD98059 treated 32°C IR mice were significantly higher than L-NAME and compound C treated 32°C IR mice. Tubular cell detachment, necrosis and TUNEL positive cells in kidneys of cold IR mice(32°C) were significantly higher than those of untreated cold IR mice with PD 98059.

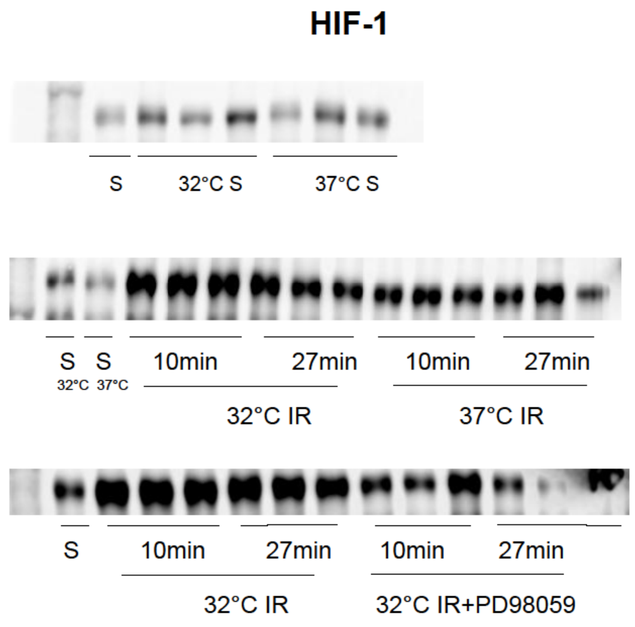

Figure 3. The level of HIF-1 was significantly decreased in the kidney of warm IR mice. PD98059 decreases the level of HIF-1 in the kidney of PD98059 treated cold IR mice.

CONCLUSIONS

In conclusion, HIF-1 preservation induced by ERK phosphorylation may be involved in hypothermic protection of renal ischemia-reperfusion injury.