

## Preservation of Hypoxia-inducible Factor-1 is Involved in Hypothermic Protection of Renal Ischemia-Reperfusion Injury

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**Background:** Although hypothermia attenuates renal injury induced by ischemia-reperfusion (IR), precise molecular pathways have not been known yet. Our previous study showed ERK phosphorylation 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 immunohistochemical 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:** Serum creatinine (s-Cr), tissue injury score, and 8-OHdG and TUNEL positive cells in cold IR mice were significantly lower than those of warm IR mice (all,  $p < 0.01$ ). s-Cr, and tissue injury score, 8-OHdG and TUNEL positive cells in kidneys of PD98059 treated cold IR mice were significantly higher than those of untreated cold IR mice (all,  $p < 0.05$ ). Renal HIF-1, PGC 1-alpha, and AMPK expression were significantly increased in the kidneys of cold ischemic mice at 10min and 27min after both renal artery clamping compared to sham operated mice. PD98059 treatment in cold IR mice decreased renal HIF-1 significantly ( $p < 0.01$ ). However, PGC-1 alpha and AMPK were not changed.

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

**Key Words:** HIF-1, IR injury, Hypothermia,  
HIF-1, Ischemia reperfusion injury, Hypothermia