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**CO releasing molecule-2 ameliorates acute kidney injury through mitochondrial fitness**

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**Objectives:** Acute kidney injury (AKI) is responsible for about 2 million deaths each year worldwide, and its incidence is rising. In addition, a strong link between AKI and chronic kidney disease has been established by recent epidemic studies. Mitochondrial injury is regarded as a hallmark of AKI, while carbon monoxide (CO) rescues mice from lethal sepsis by supporting mitochondrial energetic metabolism and activating mitochondrial biogenesis. Thus, the present study investigated the kidney protective mechanism of CO releasing molecule2 (CORM2) focusing on mitochondrial dysfunction using LPS-induced AKI mouse model.

**Methods:** Male C57BL/6J mice were administrated with LPS (15 mg/kg) to induce AKI, and i) preventive as well as ii) therapeutic effects of CORM2 (30 mg/kg) were determined. In addition, the role of heme oxygenase-1 (HO-1) was determined utilizing hemin (HO-1 inducer) and ZnPP (HO-1 inhibitor) in proximal tubular epithelial (mProx) cells. Plasma creatinine and cystatin C were measured, and kidney tissues or cells were used for mRNA and protein analysis.

**Results:** Administration of LPS induced kidney injury, inflammation, and mitochondrial dysfunction in mice. CORM2 showed not only preventive but also therapeutic effect on LPS-induced kidney injury, inflammation, and mitochondrial dysregulation in mice. Interestingly, both preventive and therapeutic treatment of CORM2 increased HO-1 expression and its related genes in AKI mice. CORM2 or hemin also attenuated LPS-induced inflammation and mitochondrial dysregulation in mProx cells, while pharmacological inhibition of HO-1 using ZnPP abrogated CORM2 or hemin effects.

**Conclusions:** These results demonstrate that CORM2 may protect AKI in mice through HO-1-mitochondrial fitness.