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NOX-selective inhibition attenuates renal ischemia-reperfusion injury via inhibition of ROS mediated ERK signaling

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Objectives: Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs) are important sources of reactive oxygen species (ROS) causing tissue injury. Inhibition of NOX shows anti-oxidative stress effect though regulating the ROS generation. This study evaluated the protective effects of NOX-selective inhibition against ischemia-reperfusion injury (IRI) mice and the H_2O_2-induced oxidative stress in MDCK cells.

Methods: C57BL/6 mice were injected intraperitoneally with 60mg/kg of ML171, a selective NOX-inhibitor, or vehicle at one time and renal ischemia-reperfusion was induced by clamping bilateral renal vascular pedicles for 30 min. MDCK cells were incubated with H_2O_2 (1.4mM) for 1 hour to induce oxidative stress and treated with ML171 (1 and 2.5μM). Kidney injury was estimated by using renal function test and histology. NOX expression, oxidative stress markers, apoptosis assay, and MAPK pathway were also evaluated in kidney tissues and MDCK cells.

Results:

IRI deteriorated renal function and increased ROS production such as H_2O_2 and DCFDA in kidney tissues, whereas treatment of ML171 significantly attenuated the IRI-mediated injuries. Intraperitoneal ML171 reversed decreased Bcl-2 and increased caspase 3 activity. ML171 also decreased the expression of NOX1, NOX2, and p40 induced by H_2O_2 treatment in MDCK cells. H_2O_2 evoked changes in oxidative stress-related enzymes of SOD and GXP production, which was mitigated by ML171 treatment. ML171 caused significant increase in the Bcl-2 level and decrease in caspase-3 activity. Among the MAPK pathways, ML171 affected ERK signaling by the phosphorylation of ERK in kidney tissues and tubular cells.

Conclusions: Our data provided that NOX-selective inhibition by ML171 attenuated renal ischemia-reperfusion injury via inhibition of ROS mediated ERK signaling. Selective inhibition of NOX could be a potential therapeutic target for acute kidney injury associated with ROS generation and subsequent apoptosis.