KSN 2016 Abstract Submission

Acute Kidney Injury

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Pharmacologic inhibition of NADPH Oxidase4/Nox4 provides renoprotection in contrast induced nephropathy

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Background: Contrast induced nephropathy may occur, in part, as a result of intrarenal oxidative stress. NADPH oxidases are important sources of reactive oxygen species (ROS). Among various type of NADPH oxidases, Nox4 is expressed predominantly in rodent kidney. The aim of the present study was to assess the effect of Nox4 inhibition on the prevention of contrast induced nephropathy (CIN).

Methods: Using HK-2 cells, Nox4 mRNA and protein were determined after exposure to iohexol with/without pretreatment of the most specific Nox1/4 inhibitor, GKT137831. Caspase3/7 activity, DHE stain and amplex red activity were also measured. Proinflammatory and apoptotic markers (pNFkB/NFkB, pp38/p38, pJNK/JNK, pERK/ERK and pcleaved caspase/caspase) were measured for investigation of intracellular pathway associated with Nox4. In addition, the effect of Nox4 inhibition were evaluated in mice model of CIN.

Results: The expression of Nox4 in HK-2 cells significantly increased by iohexol exposure. Pretreatment of GKT137831 resulted in reduced production of ROS, down regulation of proinflammatory marker (p38), that are implicated in CIN, reduced caspase 3/7 activity and increased cellular survival in iohexol exposed HK-2 cells. Silencing of the Nox4 gene replicated theses effects by down regulation of proinflammatory markers. In CIN mice model, pretreatment with GKT137831 resulted in an attenuated vacuolar degeneration, tubular epithelial cell shedding, cellular cast formation and tubular dilatation.

Conclusion: Collectively, these results identify Nox4 as a key source of ROS responsible for kidney injury in CIN and provide proof of principle for an innovative small molecule approach to prevent contrast induced nephropathy.

Table:

Keywords: contrast induced nephropathy , Nox4, reactive oxygen species