NECROSIS MODULATER NECROX-7 ATTENUATES CISPLATIN NEPHROTOXICITY

Young Rok Ham[1], Jin Young Jeong[2], Dae Eun Choi[1], Hong Jin Bae[1], Ki Rya ng Na[1], Chang Hun Song[1], and Ji Won Lee[3]

•[1] Nephrology, Chungnam National University, Daejeon, Korea, Republic Of
•[2] Department of Medical Science, Chungnam National University, Daejeon, Korea, Republic Of
•[3] Pediatric Nephrology, Chunnam National University, Daejeon, Korea, Republic Of

충남대학교병원
CHUNGNAM NATIONAL UNIVERSITY HOSPITAL

INTRODUCTION

Reactive oxygen species (ROS) generation, apoptosis, and necrosis play a role in cisplatin induced nephrotoxicity. LG life sciences developed a novel class of small molecule mitochondrial ROS scavenger NecroX series that can reduce reactive oxygen species and necroptosis pathway. We therefore investigated the effect of NecroX-7 on cisplatin nephrotoxicity in mice.

METHODS

C57BL/6 mice were divided into 4 groups; normal control group (n=5), NecroX-7 treated control group (n=5), vehicle with cisplatin (15mg/kg, intraperitoneal injection) treated group (n=9), and NecroX-7 (2mg/kg, intraperitoneal injection) with cisplatin treated group (n=9). We measured BUN and serum creatinine. We examined 8-OH deoxyguanosine, RIP1, RIP3, MLKL, and light microscopic findings (H&E and PAS stain).

RESULTS

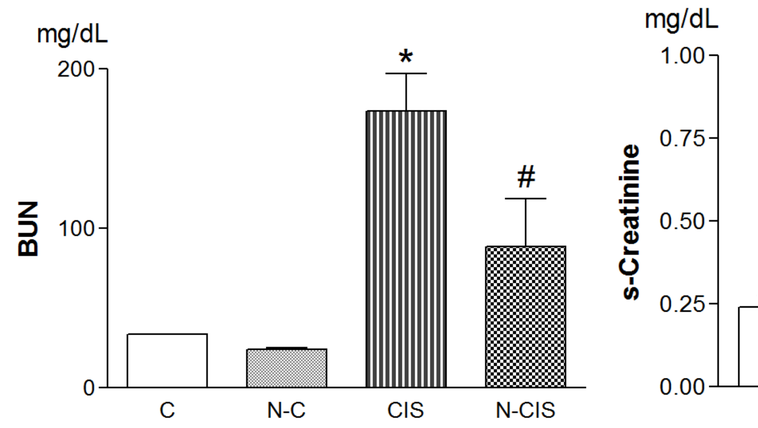

Figure 1. The levels of BUN and serum creatinine in NecroX-7 with cisplatin treated mice were significantly lower than that of vehicle with cisplatin treated mice. CIS: cisplatin treated group, LC-CIS: NecroX-7 treated cisplatin treated group (*p<0.05>)

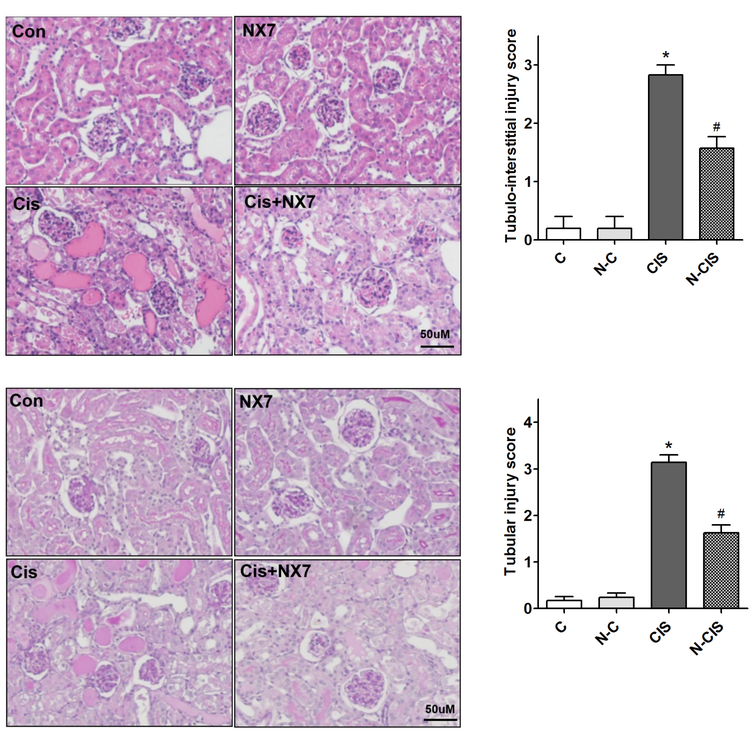

Figure 2. Representative kidney section stained for hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS). (A) H&E stain, NecroX-7 treatment significantly reduced the cell debri, tubular necrosis, and inflammatory cells in cisplatin treated mice kidneys. Original magnification, 200×. (B) PAS stain. NecroX-7 treatment reduced necrotized tubules, cast formation, loss of brush border, and dilated tubules in cisplatin treated mice. Original magnification, 200×. Con: control group, Nx7 necroX-7 with control group, CIS: cisplatin treated group, LC-CIS:NecroX-7 treated cisplatin treated group

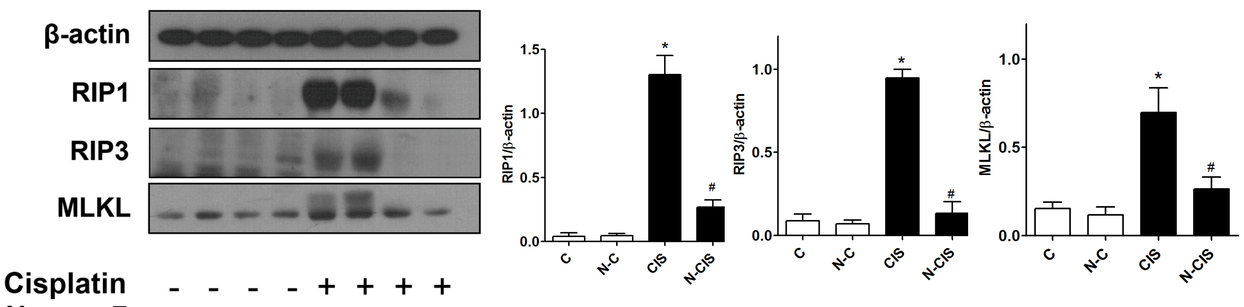

Figure 3. Representative western blot of necroptosis signals. NecroX-7 treatment significantly decreased RIP1, RIP3 and MLKL expression in cisplatin treated mice kidney.

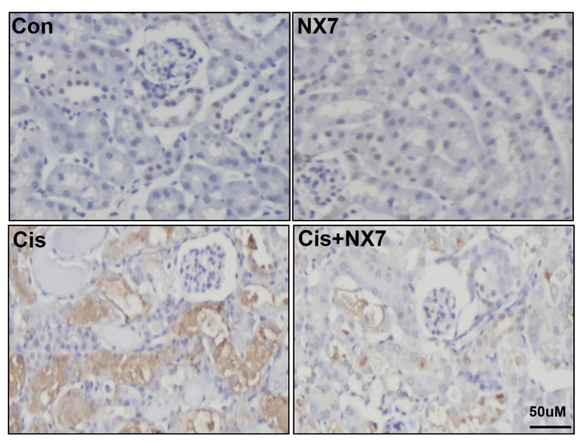

Figure 4. Representative picture of TUNEL. NecroX-7 significantly reduced TUNEL positive cells in cisplatin treated mice. Con: control group, Nx7 necroX-7 with control group, CIS: cisplatin treated group, LC-CIS:NecroX-7 treated cisplatin treated group

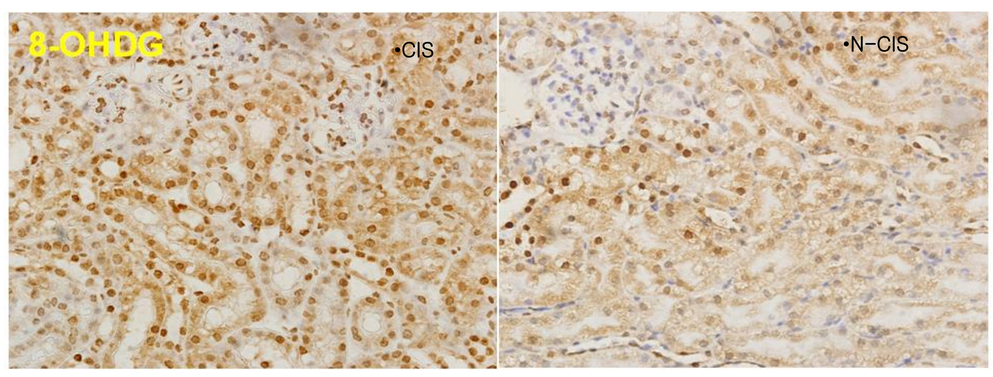

Figure 5. Representative picture of 8-OHDG. NecroX-7 significantly reduced renal tubular epithelial cell necrosis and detachment in cisplatin treated mice. NecroX-7 significantly reduced 8-OH deoxyguanosine positive cells in cisplatin treated mice. CIS: cisplatin treated group, LC-CIS:NecroX-7 treated cisplatin treated group

CONCLUSION

NecroX-7 treatment reduced necroptosis in cisplatin nephrotoxicity and reduced the cisplatin induced renal injury.

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