T-TYPE CALCIUM CHANNEL BLOCKER ATTENUATES RENAL FIBROSIS IN MICE WITH UNILATERAL URETERAL OBSTRUCTIVE NEPHROPATHY VIA ACTIVATION OF THE NRF2 ANTIOXIDANT PATHWAY

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Introduction

Role of Calcium Channel Blockers (CCBs) in the Progression of Renal Injury

- L-type CCBs
  - Fail to correct glomerular hypertension
  - Dihydropyridines-class: deleterious effect in renal diseases
    - ↑ proteinuria and glomerulosclerosis
- T-type CCBs
  - ↓ Glomerular hypertension
  - ↓ Proteinuria

Keio J Med 2010;59:84-95

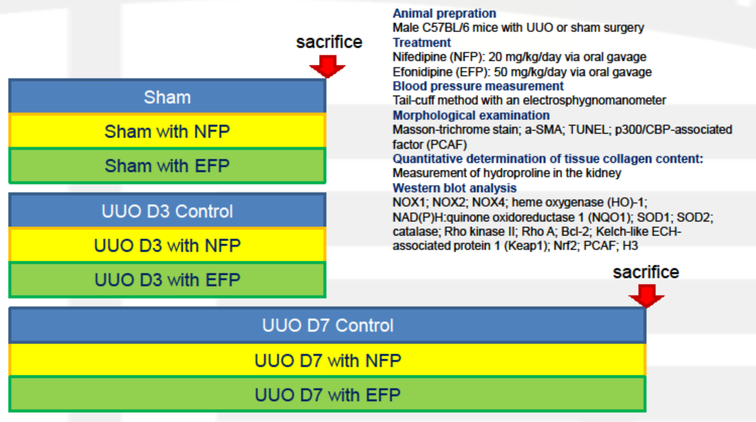
Proposed Mechanisms for T-type CCB-induced Renoprotection

- Renoprotective action of T-type CCBs is mediated by multifaceted pathways
  - Hemodynamic factor
  - Hormonal factor
  - Anti-inflammatory factor
  - Anti-oxidative stress factor?

Purpose

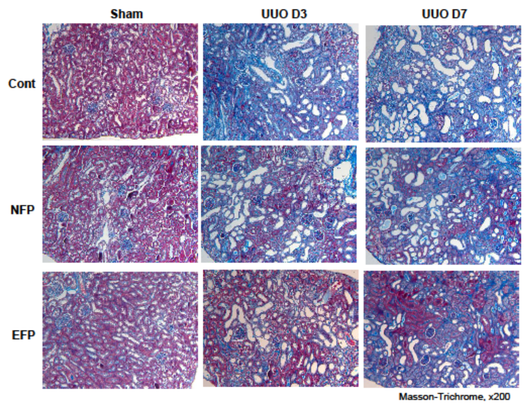
- To investigate whether the renoprotective effect of T-type calcium channel blocker is associated with modulation of the signaling of oxidative stress-induced renal fibrosis

Methods

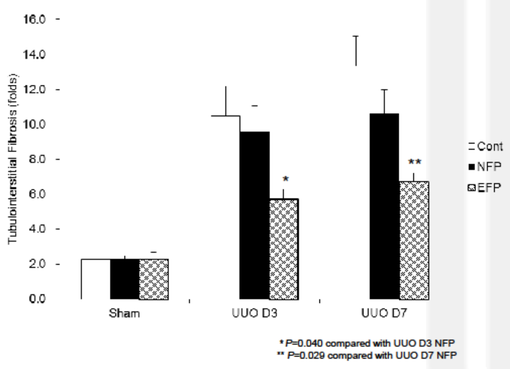


Results

Trichrome

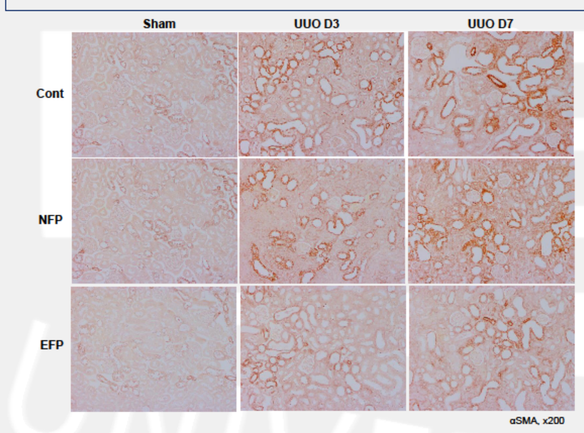


Masson-Trichrome, x200

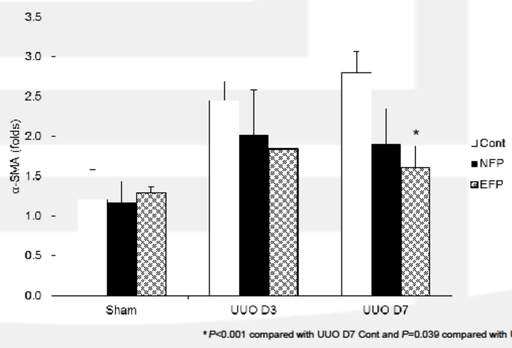


* *P*=0.040 compared with UUO D3 NFP
** *P*=0.029 compared with UUO D7 NFP

α-SMA

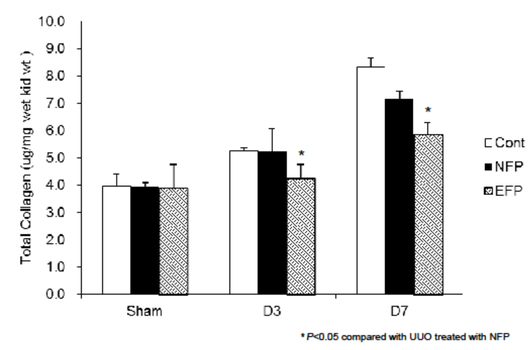


αSMA, x200



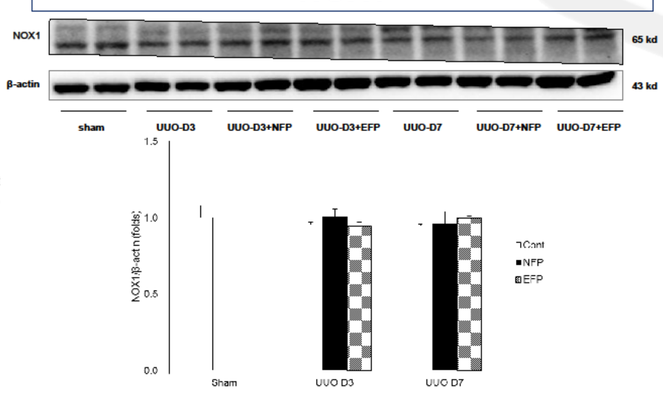
* *P*<0.001 compared with UUO D7 Cont and *P*=0.039 compared with UUO D7 NFP

Total Collagen

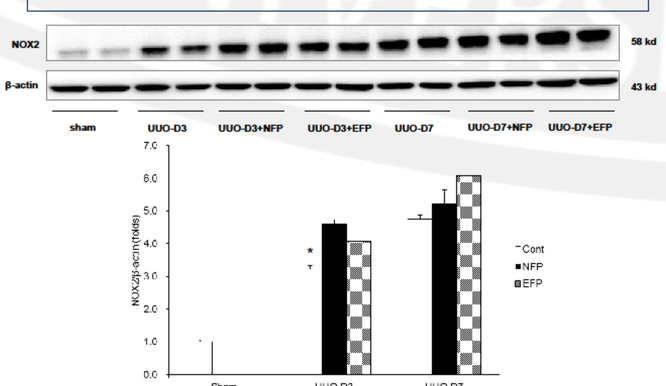


* *P*<0.05 compared with UUO treated with NFP

NOX1

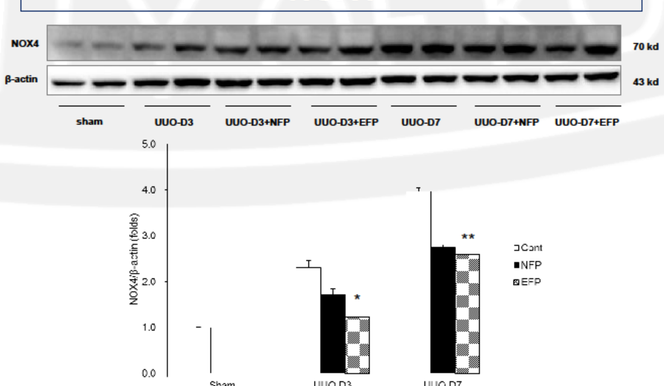


NOX2



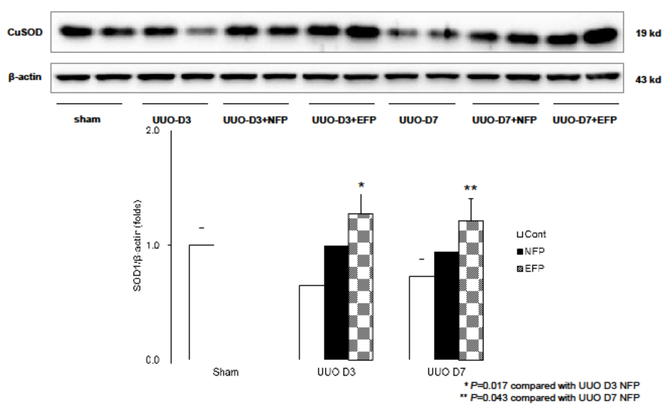
* *P*<0.001 compared with UUO D3 NFP and *P*=0.001 compared with UUO D3 EFP

NOX4



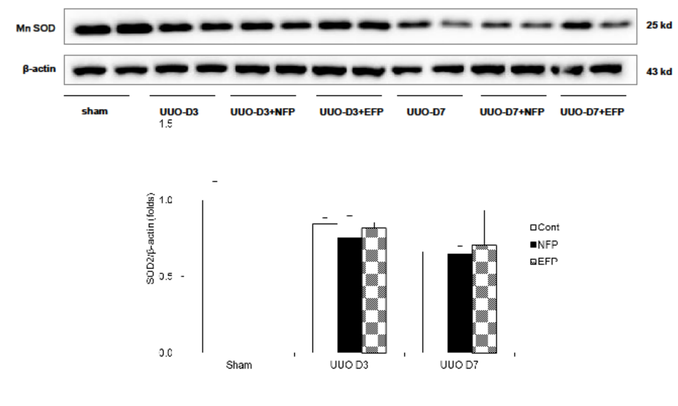
* *P*=0.017 compared with UUO D3 Cont
** *P*=0.002 compared with UUO D7 Cont

SOD1

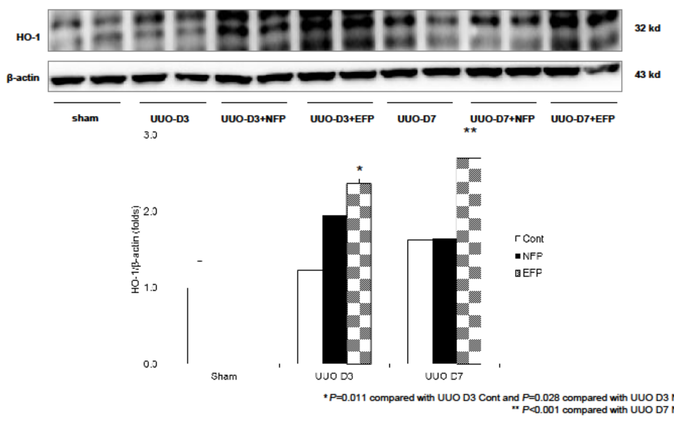


* *P*=0.017 compared with UUO D3 NFP
** *P*=0.043 compared with UUO D7 NFP

SOD2

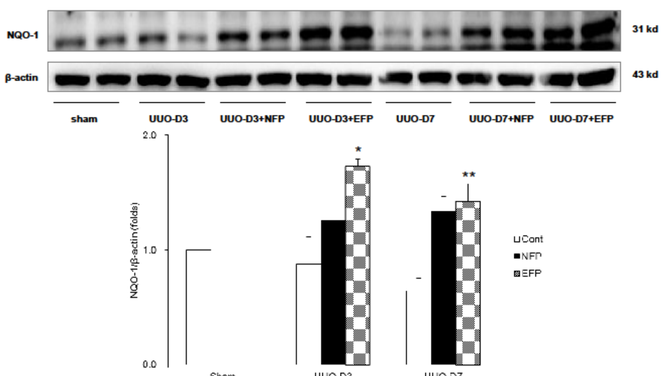


HO-1



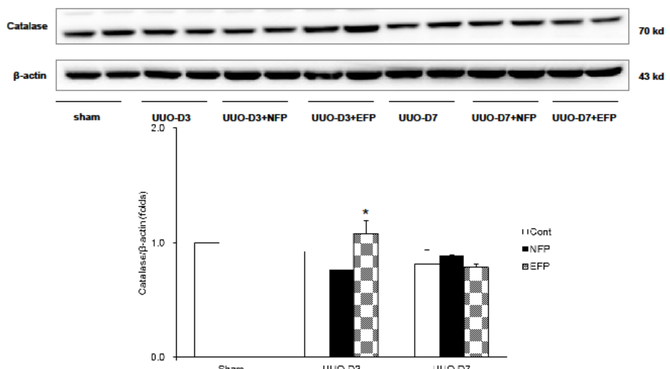
* *P*=0.011 compared with UUO D3 Cont and *P*=0.028 compared with UUO D3 NFP
** *P*<0.001 compared with UUO D7 NFP

NQO-1



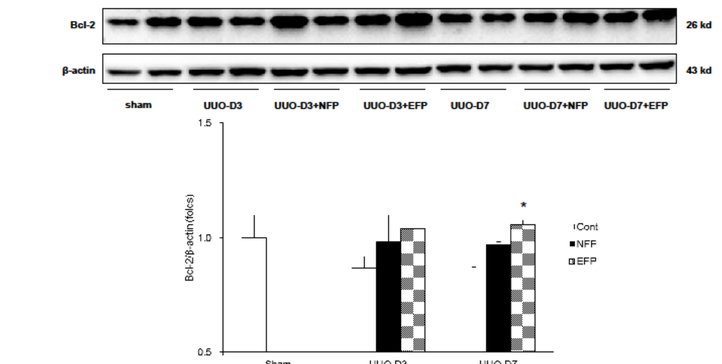
* *P*=0.048 compared with UUO D3 NFP
** *P*=0.015 compared with UUO D7 Cont

Catalase



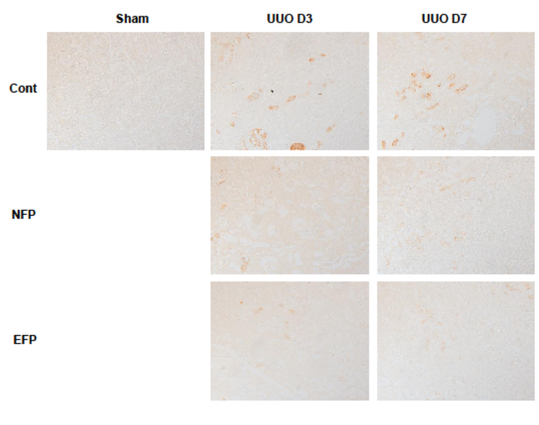
* *P*=0.013 compared with UUO D3 Cont and *P*=0.006 compared with UUO D3 NFP

Bcl-2



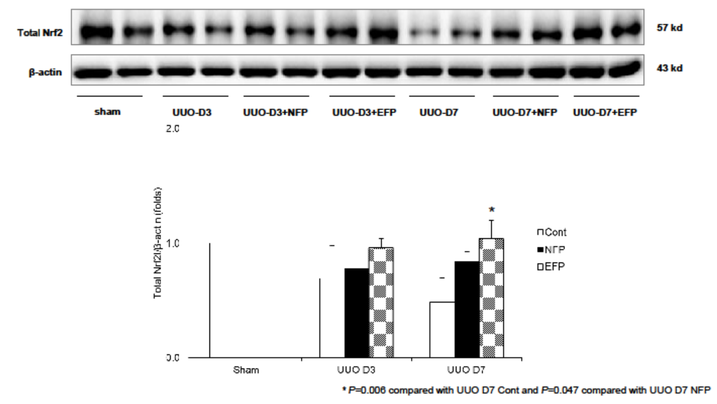
* *P*=0.046 compared with UUO D7 NFP

p300/CBP-associated factor (PCAF)



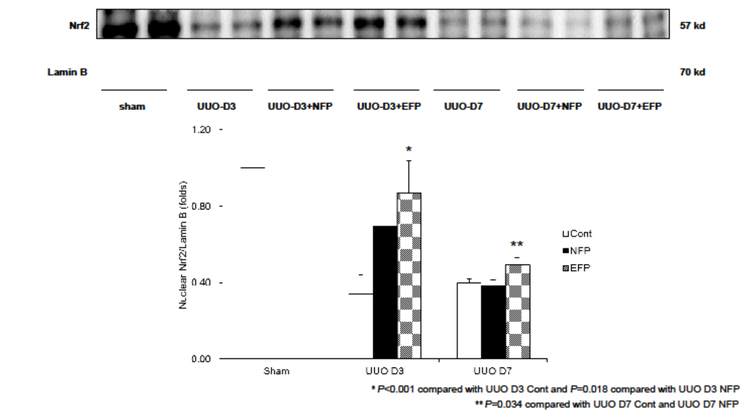
PCAF, x200

Total Nrf2



* *P*=0.006 compared with UUO D7 Cont and *P*=0.047 compared with UUO D7 NFP

Nuclear Nrf2



* *P*<0.001 compared with UUO D3 Cont and *P*=0.018 compared with UUO D3 NFP
** *P*=0.034 compared with UUO D7 Cont and UUO D7 NFP

Summary

- Renal interstitial fibrosis, inflammation and apoptosis in the obstructed kidneys were suppressed more efficiently by nonhypotensive dose of T-type calcium channel blocker than by one of L-type calcium channel blocker.
- T-type calcium channel blocker promoted the expression of anti-oxidant enzymes which would be induced by activation of Nrf2 including enhancement of nuclear translocation of cytosolic Nrf2.

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