

T형 칼슘통로차단제의 Nrf2-항산화효소 경로의 활성화를 통한 신장 섬유화의 억제 효과에 대한 연구

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정성진, 김수정, 김민영, 고은실, 김성준, 윤혜은, 박철휘, 장윤식, 신석준

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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Background: Besides the effect of treatment in high blood pressure, T-type calcium channel blocker has been reported to exert a renoprotective effect in experimental models with renal fibrosis. This may be in part due to the suppression of oxidative stress. However, the exact mechanism of T-type calcium channel blocker on tubulointerstitial fibrosis has not been fully elucidated. In the present study, we investigated whether the renoprotective effect of T-type calcium channel blocker is associated with modulation of the signaling of oxidative stress-induced renal fibrosis.

Methods: Treatment with a nonhypotensive dose of efonidipine, a T-type calcium channel blocker, or nifedipine, an L-type channel blocker, was initiated one day before unilateral ureteral obstruction (UUO) in C57BL6/J mice, and was continued until 3 and 7 days after UUO. Markers of renal fibrosis and oxidative stress were evaluated.

Results: In the obstructed kidneys of UUO mice, treatment with efonidipine significantly attenuated interstitial fibrosis, collagen deposition and inflammation increased by UUO creation compared with treatment with nifedipine. Additionally, efonidipine significantly increased the expression of antioxidant enzymes such as HO-1, NQO1, catalase and SOD1. Increased apoptotic cell death and decreased Bcl-2 expression in the obstructed kidneys were also significantly ameliorated by treatment with efonidipine. These beneficial effects of efonidipine were attributed to the increased nuclear expression of nuclear factor-erythroid-2-related factor 2 (Nrf2) on UUO day 3 and the increased expressions of both total and nuclear Nrf2 with elevated Kelch-like ECH-associated protein 1 on UUO day 7, suggesting that efonidipine would promote activation of Nrf2 differently depending time course after UUO. In contrast, nifedipine had little effect on antioxidant enzymes, anti-apoptotic protein and Nrf2 signaling.

Conclusions: These results show that T-type calcium channel blocker may exert beneficial effects in renal interstitial fibrosis by activating Nrf2 and subsequent antioxidant enzymes.

Key Words: 칼슘통로차단제, 신장섬유화, 산화스트레스

Calcium channel blocker, Renal fibrosis, Oxidative stress