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LJ-1888, a Selective Inhibitor of A3 Adenosine Receptor, Prevents Unilateral Ureteral Obstruction-induced Renal Fibrosis

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Introduction and aims: The incidence and prevalence of chronic kidney disease (CKD) is increasing worldwide. The current pharmacological treatment for CKD is, however, limited to the use of renin-angiotensin system (RAS) inhibitors. Adenosine is known to be present in a normal kidney and is significantly elevated in response to the cellular damage. All four known subtypes of adenosine receptors (A1AR, A2AAR, A2BAR, A3AR) are expressed in the kidney, but the function of A3AR is not fully understood. Only a few study reported that A3AR may play an important role in acute renal failure. The present study was performed to investigate the therapeutic effect of LJ-1888 which is the newly developed potent, selective, species-independent, and orally active A3AR antagonist on the unilateral ureteral obstruction (UUO)-induced renal fibrosis.

Methods: Eight-week-old male SD rats were used. LJ-1888 was prepared as a suspension in 0.25% carboxymethyl cellulose (CMC) and administered by oral gavage at a dose of either 1 or 10 mg/kg per day. The control group was administered an equal volume of 0.25% CMC by gavage. In all groups, medication was started 5 days before surgery and continued until sacrifice. UUO was performed under tiletamine/zolazepam-induced anesthesia. The left ureter was visualized following a flank incision, ligated with silk (4/0) at two locations and cut between ligatures to prevent urinary tract infection. At 5 days after the induction of UUO, rats were sacrificed, and kidneys were harvested for morphological, mRNA, and protein analysis.

Results: In control group, renal TGF-β1, α-SMA, fibronectin, and collagen I expression were significantly upregulated in obstructive kidneys compared to sham kidneys. In contrast, E-cadherin protein expression was not changed. Treatment with LJ-1888 effectively inhibited elevation of TGF-β1, α-SMA, fibronectin, and collagen I expression in a dose dependent manner. Masson' s trichrome staining also revealed that LJ-1888 treatment effectively reduced collagen accumulation induced by UUO in the interstitial area.

Conclusions: Our data demonstrated that pretreatment with LJ-1888 effectively inhibited UUO-induced renal injury and suggest that LJ-1888 may become a new therapeutic modality in renal interstitial fibrosis.

Key Words: 아데노신 수용체, 요로편측폐쇄, A3AR 길항제
Adenosine receptor, UUO, A3AR antagonist