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The comparative effect of LJ-2698, a highly selective adenosine 3 receptor antagonist and angiotensin receptor blockade on diabetic nephropathy in streptozotocin-induced type 1 diabetic mice

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Background: Concentration of adenosine in normal kidney increases markedly in response to cellular damage such as hypoxic injury. Extracellular adenosine binds four adenosine receptor (AR) subtypes including A₁, A_{2A}, A_{2B} and A_{3AR}. All four ARs has been detected in renal tissues, and A_{3AR} is known to be up-regulated during renal injury. A recent study reported that A_{3AR} antagonist, LJ1888, attenuated the progression of renal fibrosis in UUO model. Therefore, we investigated the comparative effect of a novel A_{3AR} antagonist LJ-2698 and L158809 (ARB) and their combination on diabetic nephropathy in streptozotocin-induced type 1 diabetic mice.

Methods: Type 1 diabetes was developed using STZ injection (50mg/kg IP for 5days) in C57BL6 mice. LJ-2698 was administered at a dose of 10mg/kg/day by gavage for 3months. To compare the effects of LJ-2698 with ARB, other group was treated with LC158809 (1.5mg/kg/d) or treated with both LJ-2698 and LC158809 for 12 weeks. To further define the mechanism of LJ-2698, we performed in vitro experiments using podocyte.

Results: As expected, STZ mice showed significantly high levels of glucose and HbA1c, and decreased body weight. LJ-2698 and ARB did not induce any significant changes in metabolic parameters such as plasma insulin levels, HOMA-IR, OGTT and ITT. Interestingly, LJ-2698 significantly decreased plasma and urinary oxidative stress markers determined by 8-isoprostane levels, which levels were not decreased with ARB. Urinary albumin excretion showed a significant decrease in both LJ-2698 and ARB group with a similar potency, and there was an additive decrease in combined treatment with LJ-2698 and ARB group. In addition, urinary nephrin excretion was also significantly decreased in both LJ-2698 and ARB group. In cultured podocytes, A_{3AR} expression was significantly upregulated in high glucose (HG), palmitates (PA) and angiotensin-II (Ang-II) treated conditions. Prior treatment with LJ-2698 markedly suppressed HG, PA and Ang-II-induced activation of TGF β 1, MCP-1 and type IV collagen synthesis.

Conclusion: Our results provide evidence that A_{3AR} antagonist shows similar renoprotective effects with ARB through protection of podocyte injury. These findings suggest that targeting A_{3AR} may have a new promising potential in diabetic nephropathy.

Keywords: adenosine 3 receptor antagonist, angiotensin II receptor blockade, diabetic nephropathy