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A novel TGF-β type I receptor inhibitor EW-7197 ameliorates high glucose-induced podocyte injury

Ah Reum Jeong[1], Jeong Suk Jang[1], So Young Kim[1], Dae-Kee Kim[2], Eun Young Lee[1]
[1]Department of Internal Medicine-Nephrology, Soonchunhyang University Cheonan Hospital, Korea, Republic of
[2]Department of College of Pharmacy, Ewha Womans University, Korea, Republic of

Objectives: Diabetic Nephropathy is a major complication of both type 1 and type 2 diabetes leading to end-stage renal failure in worldwide. Podocyte injury and loss are important in the pathogenesis and progression of diabetic nephropathy. Recently, it has been reported EW-7197, a small-molecule inhibitor of TGF-β type I receptor [activin receptor-like kinase 5 (ALK5)] has anti-fibrosis and anti-cancer activities. However, the effects of EW-7197 in diabetic nephropathy have not yet been fully elucidated. Thus, we investigated whether EW-7197 exhibits therapeutic potential on high glucose-induced podocyte injury.

Methods: We used immortalized mouse podocytes for *in vitro* system. High glucose was used to induce diabetic mimic condition. Podocytes were incubated with normal glucose (5.5 mM) and high glucose (30 mM) in the presence or absence of EW-7197 (500 nM) for 24 hrs. Western blot and quantitative real time-PCR, and immunofluorescence analysis were carried out to evaluate the effects of EW-7197 on high glucose-induced morphological and functional injury of podocytes.

Results: High glucose-induced podocyte dysfunction and apoptosis were ameliorated by EW-7197. Anti-oxidative markers were significantly decreased in high glucose-treated podocytes compared to control, whereas EW-7197 treatment significantly increased those expressions. High glucose treatment increased a substantial degree of NOX4 activity and ROS generation in podocytes, which were almost completely suppressed by EW-7197. Also, elevated expressions of ER stress markers were diminished by EW-7197 treatment. High glucose promoted expressions of inflammatory cytokines, which were inhibited by EW-7197. Treatment of EW-7197 markedly attenuates high glucose-induced up-regulation of TGF-β1 and fibronectin. Moreover, high glucose-mediated F-actin rearrangement of podocytes was recovered significantly by EW-7197 treatment.

Conclusions: These results suggest that EW-7197 may have a novel therapeutic effects on high glucose-induced podocyte injury.