Abstract Type : Poster
Presentation No. : PDO 019

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

Ah Reum Jeong1, Jeong Suk Jang1, So Young Kim1, Dae-Kee Kim2, Eun Young Lee1
1Department of Internal Medicine-Nephrology, Soonchunhyang University Cheonan Hospital, Korea, Republic of
2Department 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.