B28

Effect of ALT-711, an "AGE Cross-link breaker", on Renal Expression of NADPH Oxidase in db/db Mice

Ewha Woman University, College of Pharmacy,
Hyonam Kidney Laboratory, *Soon Chun Hyang University*[*],
Department of Anatomy, College of Medicine, The Catholic University of Korea[†], *Korea*
Department of Biochemistry, Kumamoto Universtiy School of Medicine, Kumamoto, Japan[‡]

Hunjoo Ha · Min Kyung Kwon[*] · Wan Young Kim[†] · Jin Kim[†]
Ryoji Nagai[‡] · Seikoh Horiuchi[‡] · Hi Bahl Lee[*]

Background : Oxidative stress plays an important role in the development and progression of diabetic renal injury. NADPH oxidase has recently been suggested to be a major source for reactive oxygen species (ROS) in streptozotocin-induced diabetic kidney. Advanced glycation end-products (AGE) may increase oxidative stress through activation of NADPH oxidase. We, therefore, examined the effects of ALT-711 [3-(2-oxo-2-phenyl)ethyl-4,5-dimethylthiazolium chloride], an AGE cross-link breaker, on renal expression of NADPH oxidase in db/db mice, a model of type 2 diabetes.

Methods : ALT-711 (2 mg/kg/day) or saline was administered intraperitoneally to 8-week-old diabetic db/db mice with stable hyperglycemia and control db/m mice for 12 weeks. Urinary albumin excretion was measured by ELISA and normalized by creatinine. Glomerular volume (VG) and fractional mesangial area (FMA %) were quantitated using a computer-assisted color image analyzer. Fibronectin (FN) and pentosidine protein expression in isolated glomeruli were analyzed by Western blot analysis. Subunits of NADPH oxidase in cortical tubules were measured by real-time RT-PCR.

Results : Untreated diabetic db/db mice at 20 weeks of age had significantly increased VG, FMA, urinary albumin excretion rate (UAE), and urinary LPO compared to db/m mice of the same age. Glomerular FN increased 8-fold in db/db mice compared to db/m mice, pentosidine by 1.6-fold, NOX-2 mRNA by 2-fold, p47phox by 1.5-fold, and p67phox by 1.5-fold. NOX-4 mRNA expression in db/db mice was not different compared to db/m mice. Treatment with ALT-711 effectively ameliorated all these changes in db/db mice without an effect on plasma glucose level.

Conclusion : This study provide evidence data AGE may increase oxidative stress in the kidney through upregulating NADPH oxidase and ALT-711 may prove to be a novel therapeutic agent in renal injury of type 2 diabetes.