INHIBITION OF PRONGF PATHWAY RESTORES ERECTILE DYSFUNCTION THROUGH DUAL ANGIOPGENIC AND NEUROTROPHIC EFFECTS IN THE DIABETIC MOUSE

Nhat Minh Nguyen, Kang-Moong Song, Kalyan Ghatak, Mi-Hye Kwon, In-Rae Cho, Won Hee Park, Guo Nan Yin, Ji-Kan Ryu, and Jun-Kyu Suh*
National Research Center for Sexual Medicine and Department of Urology, Inha University School of Medicine, Incheon, Korea

Introduction and Objective: Patients with diabetic erectile dysfunction (ED) often respond poorly to oral PDE5 inhibitors due to a lack of bioavailable nitric oxide from severe endothelial and neuronal dysfunction. ProNGF and its receptor p75NTR are known to be up-regulated in diabetic condition and to induce endothelial cell apoptosis and neuronal degeneration in the retina. The aim of the study was to investigate the role of proNGF/p75NTR signaling pathway and effectiveness of proNGF neutralizing antibody (proNGFab) in reversing erectile dysfunction in streptozotocin-induced diabetic mice.

Methods: Diabetes was induced by streptozotocin injection of streptozotocin (55 mg/kg) in 8-week-old C57BL/6J male mice for 5 consecutive days. At 8 weeks after the induction of diabetes, the animals were distributed into 3 groups: controls, streptozotocin-induced diabetic mice receiving repeated intramuscular injections of PBS (days 0 and 1, 20 µl of proNGFab (days 3 and 3, 20 µl in 20 µl of PBS). Each group was harvester for histological and biochemical studies. We also examined the effect of proNGFab and p75NTRA in primary cultured mouse cavernous endothelial cells, pericytes and major pelvic ganglia.

Results: The expression of proNGF and p75NTR was up-regulated in diabetic patients and STZ-induced diabetic mice. Intravenous injection of proNGF-As significantly increased cavernous endothelial cell content and endothelial cell-cell junction proteins, decreased endothelial cell apoptosis, and restored neuronal cell content in the cavernous tissue of diabetic mice. Under the high glucose condition, proNGFab and p75NTRAb either alone or in combination showed formation in mouse cavernous endothelial cells and enhanced erectile responses in major pelvic ganglia culture.

Conclusions: Our findings suggest that proNGF/p75NTR signaling pathway played an important role in pathophysiology of diabetic erectile dysfunction and inhibition of proNGF/p75NTR pathway is a promising therapeutic strategy for diabetic ED.

Keywords: erectile dysfunction, diabetes mellitus, proNGF, p75NTR

Abstract Number MP43-06