

S-D15

Dipeptidyl Peptidase IV Inhibitor의 투여가 tacrolimus로 유발된 당뇨에서 췌장손상에 미치는 영향

가톨릭대학교 서울성모병원 장기이식연구소¹, 신장내과², 면역질환융합사업단

임선우¹, 김룡¹, 도경찬¹, 김건¹, 박상국¹, 정병하², 양철우²

Dipeptidyl Peptidase IV Inhibitor MK-0626 Attenuates Pancreatic Islet Injury in Tacrolimus-Induced Diabetic Rats

Sun Woo Lim¹, Jin Long¹, Doh Kyoung Chan¹, Jin Jian¹
Piao Shang Guo¹, Chung Byung Ha², Yang Chul Woo²

Transplant Research Center¹, Division of Nephrology Department of Internal Medicine², CRCiD
Seoul St. Mary's Hospital, The Catholic University of Korea

Background: Tacrolimus (TAC)-induced pancreatic islet injury is one of the important causes of new onset of diabetes in transplant recipients. This study was performed to evaluate whether a dipeptidyl peptidase (DPP) IV inhibitor is effective in improving TAC-induced diabetes mellitus by reducing pancreatic islet injury.

Methods: Rats were treated with TAC (1.5 mg/kg, subcutaneously) and DPP IV inhibitor MK-0626 (10 or 20 mg/kg, oral gavage) for 4 weeks. The effect of MK-0626 on TAC-induced diabetes was evaluated by assessing pancreatic islet function, histopathology. TAC-induced incretin dysfunction was also examined with the serum active glucagon like peptide (GLP)-1 level after glucose loading. Protective effect of MK-0626 was evaluated by measuring markers for oxidative stress, oxidative resistance, and apoptosis. To reveal whether enhanced GLP-1 signaling is associated with these protective effects, we measured the expression of GLP-1 receptor (GLP-1R) and effect of GLP-1 analogue exendin-4 on cell viability and oxidative stress in isolated islets.

Results: MK-0626 treatment attenuated TAC-induced pancreatic islet dysfunctions and islet morphology. TAC treatment showed defective in active GLP-1 secretion; however, MK-0626 recovered these effects. TAC treatment increased the level of 8-hydroxy-2'-deoxyguanosine (8-OHdG), number of apoptotic cell death, active caspase-3 and decreased the level of manganese superoxide dismutase and heme oxygenase-1, and MK-0626 treatment reversed these changes. MK-0626 treatment restored the expression of GLP-1R and direct exendin-4 treatment in isolated islet reduced TAC-induced cell death and 8-OHdG expression.

Conclusions: DPP IV inhibitor MK-0626 is an effective anti-diabetic agent with antioxidative and antiapoptotic properties by enhanced GLP-1 signaling in TAC-induced diabetics. These beneficial effects of DPP IV inhibitor could be helpful to a delay in the new onset of diabetes in transplant recipients.

Key Words: tacrolimus, 췌장독성, 당뇨, 산화성 스트레스
Tacrolimus, Pancreas, Toxicity, DPPIV inhibitor