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Effect of Empagliflozin on Tacrolimus-induced Pancreas Islet Dysfunction and Renal Injury

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Objectives : An inhibitor of sodium glucose co-transporter type 2 (SGLT-2) is recommended in type 2 diabetes mellitus (DM) but its use is still undetermined in Tacrolimus (TAC)-induced DM.

Methods : We evaluated the effect of empagliflozin (Em) on TAC-induced pancreatic islet dysfunction and renal injury in experimental model of TAC-induced DM and in vitro. Male Sprague Dawley rats (Charles River Technology, Seoul, Korea) weighing 200 to 220 g were housed in individual cases and allowed free access to a low-salt diet (0.05 % sodium, Teklad Premier, Madison, WI, USA) and tap water. After acclimatization and a low-salt diet for 1 week, weight-matched rats were randomized to six groups containing twelve rats each and were treated daily with TAC (1.5 mg/kg, s.c.) or vehicle (VH, olive oil, 0.3 ml, s.c.) for 3 weeks. After confirming development of TAC-induced DM, Em (5 and 10 mg/kg, oral gavage) was added for 3 weeks more. Control rats were treated with Em only.

Results : TAC induced a two-fold increase in SGLT-2 expression, while Em decreased SGLT-2 expression and further increased urinary glucose excretion compared to the TAC group. Em reduced hyperglycemia and increased plasma insulin level, pancreatic islet size and glucose-stimulated insulin secretion (GSIS) compared to the TAC group. In kidney, Em alleviated TAC-induced renal dysfunction and decreased albumin excretion and histological injury compared with the TAC group. Increased oxidative stress and apoptotic cell death by TAC was remarkably decreased with Em in serum, pancreatic and renal tissues. In vitro study, TAC decreased cell viability and increased reactive oxygen species (ROS) production in both insulin secreting beta cell derived (INS-1) and human kidney-2 (HK-2) cell lines. Addition of Em increased cell viability and decreased ROS production in HK-2 but not in INS-1 cell lines.

Conclusions : This suggests that Em is effective in controlling TAC-induced hyperglycemia and has direct protective effect on TAC-induced renal injury.

Keywords : SGLT-2 inhibitor, Empagliflozin, TAC