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Pancreatic Kallikrein Protects Against Tacrolimus-Induced Pancreatic and Renal Injuries

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Objectives: Reducing immunosuppressant-related complications have important clinical implication owing to often use this class of drugs. This study investigated whether exogenous pancreatic kallikrein (PK) treatment would confer protection in tacrolimus (TAC)-induced pancreatic and renal injuries in ways of *in vivo* and *in vitro*, since PK has protective effects against diabetes mellitus and various types of renal injury.

Methods: Establishment of TAC-induced pancreatic and renal injury was performed in male Sprague-Dawley rats by subcutaneous injection of TAC for 4 weeks, and PK was given concomitantly. The influence of PK on pancreatic injury was examined with status of blood glucose and insulin levels and pancreatic islet intact. Renoprotective effect of PK was assessed in terms of renal function, histopathology, cytokine expressions, oxidative stress, apoptotic cell death and autophagy, and AKT/PI3k/FoXo3a signaling pathway. In addition, pancreatic β cells and human HK-2 cells with TAC and PK bitherapy were also studied.

Results: PK treatment abolished pancreatic β cell apoptosis and preserved pancreatic islet size, thereby lowered blood glucose level and enhanced insulin secretion as well as glucose-stimulated insulin secretion. In the kidney, PK improved renal dysfunction and histopathological injury, which was paralleled with suppression of pro-inflammatory and pro-fibrotic cytokine expression. Increased oxidative stress, apoptotic cell death, and autophagy induced by TAC were significantly decreased with administration of PK through interfering AKT/PI3K/FoxO3a signaling pathway. The achievement of PK was attributed to upregulation of bradykinin B1R and B2R expression and overproduction of bradykinin and nitric oxide. The protective effects of PK observed in this study were annihilated by either B1R or B2R antagonist. By in vitro studies, PK improved pancreatic β and HK-2 cells viability and inhibited ROS formation.

Conclusions: PK effectively attenuates TAC-induced pancreatic and renal injuries.