PARP inhibition ameliorates nephropathy in an animal model of type 2 diabetes: focus on oxidative stress, inflammation, and fibrosis.

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Abstract

Poly(ADP-ribose) polymerase (PARP) enzyme contributes to nephropathy, a serious diabetic complication which may lead to end-stage renal disease. The study aims to investigate the effect of PARP over-activation on kidney functions in a type 2 diabetic rat model. The study also tests the therapeutic use of PARP inhibitors in diabetic nephropathy. Type 2 diabetes was induced in adult male rats by high-fructose/high-fat diet and low streptozotocin dose. Then, the PARP inhibitor 4-aminobenzamide (4-AB) was administered daily for 10 weeks. At the end, urine samples were collected to measure urine creatinine, albumin, and total proteins. PARP activity, superoxide dismutase (SOD) activity, and nitrite content were measured in kidney tissue homogenate. Glucose, fructosamine, insulin, and tumor necrosis factor-alpha (TNF-Ŭ) were measured in serum. Furthermore, histological studies, collagen deposition, and immunofluorescence of nuclear factor kappa B (NF əB) and transforming growth factor beta1 (TGF-ɓ1) were carried out. PARP enzyme activity was significantly higher in the diabetic group and was significantly reduced by 4-AB administration. Diabetic animals had clear nephropathy indicated by proteinuria and increased albumin excretion rate (AER) which were significantly decreased by PARP inhibition. In addition, PARP inhibition increased creatinine clearance in diabetic animals and reduced renal TGF-ɓ1 and glomerular fibrosis. Moreover, PARP inhibition alleviated the elevated serum TNF-Ŭ level, renal NFəB, nitrite, and the decrease in SOD activity in diabetic animals. However, PARP inhibition did not significantly affect neither hyperglycemia nor insulin sensitivity. PARP enzyme inhibition alleviates diabetic nephropathy through decreasing inflammation, oxidative stress, and renal fibrosis.

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