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A PPAR α Agonist Improves Diabetic Nephropathy in db/db Mice

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Peroxisome proliferator-activated receptor a (PPAR α) is a member of the ligand-activated nuclear receptor superfamily and plays an important role in lipid metabolism and glucose homeostasis. Specific PPAR α agonists, including fibrates such as fenofibrate, not only attenuate dyslipidemia, but also improve insulin resistance in both animal and man. Recently, PPAR α has been found to be highly expressed and involved in energy homeostasis in the kidney. The present studies were aimed at examining the effect of PPAR α activation on the development and progression of diabetic nephropathy (DN).

Sixteen male db/db mice on C57 BLKS background at 8 wks of age were divided into two groups. Control db/db mice (n=8) received control chow while the experimental group (n=8) received chow containing fenofibrate (300 mg/kg/day) for 8 weeks. Fenofibrate dramatically improved fasting blood glucose in db/db mice (170±54 vs 588 ±62 mg/dL, $p<0.001$) and HbA1C concentration (4.9±1.2 vs. 8.5±-0.8%, $p<0.001$) despite the fact that no difference in food intake between two groups was detected and the body weight was actually slightly increased in fenofibrate group towards the end of the study ($p<0.05$). Hypertrophy and hypercellularity of pancreatic islets and plasma insulin levels were also markedly improved ($p=0.002$). In addition, fenofibrate treatment significantly reduced urinary albumin excretion (13±10 vs. 283±83 mg/L/24 hours, $p=0.03$). Renal histology studies further demonstrated that glomerular hypertrophy and mesangial matrix expansion were reduced in fenofibrate-treated animals compared to those in non-treated animals. In vitro studies demonstrated that endogenous PPAR α expression in mesangial cells was suppressed by high glucose (30 Mm) treatment. Fenofibrate treatment also abolished increase type IV collagen production following high glucose treatment.

Taken together, the PPAR α agonist fenofibrate dramatically improves hyperglycemia, insulin resistance, albuminuria and glomerular fibrosis in db/db mice and may serve as a therapeutic agent for type II diabetes and diabetic nephropathy.