S-A10

당뇨병성 신증 동물 모델에서 AMPK-PGC-1α-ERR-1α 신호 전달 체계 활성화를 통한 Fenofibrate의 치료 효과

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Fenofibrate Ameliorates Diabetic Nephropathy Though the Activation of AMPK-PGC-1α-ERR-1α Signaling in db/db Mice

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The peroxisome proliferative-activate receptor-α (PPARα) is a lipid-sensing transcriptional factor that has a role in gluco-oxidative stress and lipotoxicity. AMP-kinase (AMPK) and peroxisome proliferative-activated receptor gamma coactivator (PGC)-1α is a multifunctional transcriptional protein, acts as a 'molecular switch' in pathways controlling fatty acid oxidation and oxidative stress, and may be a critical link in the pathogenesis of type 2 diabetes and metabolic syndrome associated with estrogen-related receptor (ERR)-1α. We evaluated the renoprotective effect of fenofibrate agonist lipotoxicity through the change of AMPK-PGC-1α-ERRα and their downstream PI3K-Akt-FoxOs on diabetic nephropathy in db/db mice.

Male C57 BLKS db/db mice and db/m controls at 8 weeks of age were divided to receive either a regular diet chow or a diet containing fenofibrate (0.2% wt/wt, n=6, respectively). Mice were followed for 12 weeks and were evaluated about renal functional and pathologic phenotypes and the PPARα-AMPK-PGC-1α-ERR-1α pathway.

Fenofibrate treatment slightly reduced fasting blood glucose ($p<0.05$) and HbA1c levels ($p<0.05$) in db/db mice. Fenofibrate also ameliorated albuminuria ($P<0.001$) and decreased urine volume ($p<0.001$) in db/db mice. The mesangial area expansion, inflammatory cell infiltration, and the accumulation of intra-renal free fatty acid and triglycerides were observed in db/db mice. A downregulation of PPARα suppressed AMPK-PGC-1α and ERR-1α expressions and increased PI3K-Akt-phosphorylation of FoxO3a, not FoxO1, in the kidney, which led to oxidative stress and decreases fatty acid oxidation. Treatment of fenofibrate increased the PPARα expression and subsequently activated the AMPK-PGC-1α-ERR-1α and suppressed PI3K-Akt-phosphorylation of FoxO3a signaling. In cultured mesangial cells, suppressed AMPK-PGC-1α-ERR-1α and increased PI3K-Akt-phosphorylation of FoxO3a signaling in high-glucose media reversed by fenofibrate, which was associated with decreases in oxidative stress and apoptosis.

In conclusion, the results suggest that PPARα agonist fenofibrate improves lipotoxicity through activation of the AMPK-PGC-1α-ERR-1α signaling and may be a potentially therapeutic modality for type 2 diabetic nephropathy.

Key Words: 당뇨병성 신증, fenofibrate, PGC-1α
Daibetic nephropathy, Fenofibrate, PGC-1α