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fenofibrate의 PGC-1α-ERR-1α 신호전달체계의 활성화를 통한 당뇨병성 신증의 호전

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

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Background: The peroxisome proliferative-activate receptor-α (PPARα) is a lipid-sensing transcriptional factor that has a role in gluco-oxidative stress and lipotoxicity. 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 PGC-1α-ERRα signaling on diabetic nephropathy in db/db mice.

Methods: 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). The treated db/m mice and db/db mice were administrated fenofibrate for 2 months starting at age of 12 weeks, and were evaluated about renal functional and pathologic phenotypes and the PPARα-PGC-1α-ERR-1α pathway.

Results: Fenofibrate treatment dramatically 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. There was no difference serum creatinine level in all each groups. 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 PGC-1α and ERR-1α expressions and led to increases in oxidative stress and decreases fatty acid oxidation. Treatment of fenofibrate increased the PPARα expression and subsequently activated the PGC-1α-ERR-1α signaling. The activation of PGC-1α-ERR-1α ameliorated oxidative stress and fatty acid oxidation.

Conclusion: Our results suggest that PPARα agonist fenofibrate improves lipotoxicity through activation of the PGC-1α-ERR-1α signaling in type 2 diabetic nephropathy and may be a potentially therapeutic modality to modulate PGC-1α-ERR-1α signaling to treat type 2 diabetic nephropathy.

Key Words: 당뇨병성 신증, 지방독성, PGC-1a
Diabetic nephropathy, lipotoxicity, PGC-1a