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고지방식이를 투여하여 고혈압과 신손상이 유도된 자연발생고혈압쥐에서 fenofibrate와 tempol의 PI3K/Akt/FoxO3a-산화 스트레스 신호전달계에 미치는 영향

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Fenofibrate and Tempol Prevent High-Fat Diet-Induced Hypertension and Renal Damage in Spontaneously Hypertensive Rat via PI3K/Akt/FoxO3a-Oxidative Stress Signaling Pathway

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Introduction : Phosphatidylinositol-3-OH kinase (PI3K)/protein kinase B (Akt)/forkhead box-containing protein O (FoxO) signaling pathway regulates cell metabolism, cell cycle arrest, oxidative stress, and apoptosis. We have previously demonstrated that peroxisome proliferator-activated receptor alpha (PPARalpha) activator and antioxidant have protective effect on high-fat diet-induced renal damage and hypertension in spontaneously hypertensive rat (SHR). In this study, we investigated which intracellular pathways would be involved in these protective effects in high-fat diet-induced hypertension and renal injury in SHR.

Methods : SHR and Wistar-Kyoto rat (WKY) at 8 weeks age were treated with either a normal diet (SHR-C or WKY-C group, n=6, respectively) or a high fat diet (SHR-HF or WKY-HF group, n=8, respectively) with or without fenofibrate and tempol for 12 weeks.

Results : After 12 week, body weights, intra-abdominal fat mass, and intrarenal free fatty acid and triglycerides accumulation were significantly increased in SHR-HF and WKY-HF compared to those in SHR-C and WKY-C ($p<0.05$). In SHR-HF, systolic BP and 24 hr albuminuria were significantly increased than those in SHR-C ($p<0.05$). Renal histology studies demonstrated that glomerular mesangial expansion and inflammation were significantly increased in SHR-HF. These changes were associated with decrease in intrarenal PI3K-pAkt-pFoxO3a signaling, consequently leading to oxidative stress and apoptosis, which reflected increases in 8-OH-deoxyguanosine levels in the kidney and urine and TUNEL positive cells, respectively. On the contrary, there were no such differences between WKY and WKY-HF. Interestingly, fenofibrate and tempol treatments normalized all of these abnormalities via activation of PI3K-pAkt-pFoxO3a signaling pathway, which suppressed PI3K-pAkt-pFoxO3a signaling pathway associated with the induction of intrarenal PPARalpha.

Conclusion : Fenofibrate and tempol ameliorate high-fat diet-induced hypertension and renal damage in SHR via PI3K-Akt-FoxO3a-oxidative stress. Our results suggest that PPARα activation by PPARalpha agonist or antioxidant could provide a therapeutic role in high-fat diet-induced renal damage and hypertension.

Key Words : PI3K/Akt/FoxO3a-산화 스트레스 신호전달계
PI3K/Akt/FoxO3a, Oxidative Stress, PPARalpha agonist