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Resveratrol의 당뇨병성 신병증에서 AMPK-Sirt1-PPARα-FoxOs 신호전달 계를 통한 신장 보호효과

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박훈석, 임지희, 김민영, 정성진, 신석준, 최범순, 김형욱, 김용수, 장윤식, 박철휘

Resveratrol Prevents Diabetic Nephropathy Via Activating AMPK-Sirt1-PPARα-FoxOs Pathway in db/db Mice

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Introduction: Resveratrol is a natural plant polyphenol and has protective effects in rodent models of stress and renal diseases. Resveratrol activates Sirt1 and AMPK and subsequently augments PGC-1, eNOS and FoxOs activation, which follows catabolic metabolism, mitochondrial activation, angiogenesis, and enhancing cell survival. Recently, we demonstrated that PPARα activation has protective effects on diabetic nephropathy. We hypothesized that resveratrol may have therapeutic potential for preventing renal cell apoptosis and oxidative stress, which are the main causes of renal damage in diabetic nephropathy.

Methods: Male db/db mice and db/m mice at 8 wks of age treated with or without resveratrol (20 mg/Kg) for 12 weeks. We measured urinary albumin, histological changes, oxidative markers, and intrarenal AMPK-Sirt1-PPARα-FoxO3a signaling and its target molecules.

Results: We found that the db/db mice treated with resveratrol decreased albuminuria and ameliorated glomerular matrix expansion, Col IV expression and TGF-β1 compared to the control diabetic db/db mice even under the same degree of hyperglycemia . More apoptotic renal cells and inflammatory cell infiltration were noted in the db/db mice compared to the db/m mice groups. In contrast, resveratrol also improved renal cells apoptosis and intrarenal inflammatory cell infiltration in the db/db mice. Of interest, in the db/db mice intrarenal The172 phospho-AMPK-Sirt1-PPARα expression was significant decreased compared to those of db/m mice, which was increased by resveratol treatment to the same levels or even more of db/m mice groups. Increased PI3K activity and phosphorylation of Akt and FoxO3a were found in the db/db mice. Resveratrol decreased the activity of PI3K, increased dephosphorylation of Akt and decreased phosphorylation of FoxO3a, suggesting increased FoxO3a activation, which resulted in not only a decrease in proapototic Bax but also increases in anti-apoptotic Bcl-2 and increases in SOD1 and SOD2 expressions in the kidneys. According to the changes of SOD1 and SOD2, increased renal 8-OH-dG and urinary 8-OH-dG and isoprostan were reversed by resveratrol in the db/db mice.

Conclusion: Our results suggest that resveratrol prevents diabetic nephropathy in db/db mice by activation of AMPK-Sirt1-PPARα signaling, which results in inhibition of apoptosis and oxidative stress in the kidney.

Key Words: 당뇨병성 신증, 세포자연사, PPAR알파
Apoptosis, PPARα, Dibetic nephropathy