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고혈당에서 배양된 사이간질 세포에서 thrombospondin-1 유도에 대한 α-Spinasterol의 영향

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Effect of α-Spinasterol on Induction of Thrombospondin-1 by High Glucose in Cultured Mesangial Cells

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Background: Transforming growth factor-β (TGF-β) is the central cytokine responsible for the development of diabetic nephropathy. It is recently reported that thrombospondin-1 (TSP-1) is the major activator of latent TGF-β in diabetic nephropathy in vivo. We suggested previously that α-spinasterol may be a promising therapeutic substance able to ameliorate the development and progression of diabetic nephropathy by inhibiting TGF-β production. However, it has not been investigated how α-spinasterol inhibit TGF-β production. So this study is to examine the effect of α-spinasterol on TSP-1 production and downstream target of TGF-β through TSP-1 induced by high glucose in cultured mesangial cells.

Methods: Mouse mesangial cells were incubated for 24 hour with normal (5.6 mM) or high (30 mM) glucose-containing medium in the presence or absence of α-spinasterol (1 ng/mL). Mesangial proliferation was determined by counting cell number. Real time qRT-PCR was performed to observe the TSP-1, TβRI, and TβRII mRNA expression. TSP-1, Smad2/3, TIMP2, and MMP2 protein expression in medium or cell lysate were determined by western blot. Gelatin zymography was performed for the measurement of MMP2 activity in medium.

Results: α-spinasterol inhibited the high glucose-stimulated proliferation of mouse mesangial cells, but did not affected to the growth of mouse mesangial cells cultured under normal glucose. TSP-1 mRNA expression and protein expression was increased in cultured mouse mesangial cells under the high glucose concentration. α-spinasterol attenuated TSP-1 mRNA expression and protein expression in cultured mouse mesangial cells under the high glucose. Also, α-spinasterol inhibited TSP-1 protein expression in medium of cultured mouse mesangial cells under the high glucose. Smad2/3 activity was increased in high glucose-stimulated mesangial cell, but decreased by α-spinasterol. TIMP2/MMP2 ratio in cultured medium or cell lysate was decreased by α-spinasterol. MMP2 acitivity on gelatin zymography was similar to MMP2 protein expression in same medium.

Conclusion: We demonstrated that α-spinasterol attenuated TSP-1 protein expression in cultured mouse mesangial cells under the high glucose, and resulted in regulating cell proliferation, and TIMP2/MMP2 ratio through TGF-β/Smad2/3 signaling.This result suggests that α-spinasterol may be considered as a promising future treatment option for diabetic nephropathy.

Key Words: 당뇨병성 신병증, 트롬보스폰딘-1, 사이간질 세포
Diabetic nephropathy, Mesangial cell, Thrombospondin-1