Bis 단백 결손에 의한 산화스트레스 증가가 당뇨병성 신증에 미치는 영향에 대한 연구

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Bis-Haploinsufficiency Aggravates Diabetic Nephropathy by Increasing Oxidative Stress

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Introduction: The Bis, Bcl-2 interacting death suppressor, is ubiquitously expressed in cells and has anti-stress and anti-apoptotic activity of Bcl-2. Complete inhibition of Bis protein synthesis showed early lethality associated with malnutrition. Notably, oxidative stress-induced apoptosis contributes the pathogenesis of diabetic nephropathy. We investigated the role of Bis expression on the diabetic nephropathy using bis-haploinsufficient (Bis-HT) mice.

Methods: Male bis-hetero-deficient (+/-; Bis-HT) mice and normal bis wild-type (+/+; Bis-WT) mice at 8 wks of age treated with or without low-dose streptozotocin for 5 days were divided into 6 groups. 4 weeks after the injection of streptozotocin, the superoxide dismutase (SOD) mimetic tempol was given to diabetic Bis-WT DM and Bis-HT DM mice in drinking water (20 μg/kg/day) for 8 weeks (Bis-WT DM Temp and Bis-HT DM Temp).

Results: At 12 weeks after induction of diabetes, there was an increase in Bis levels in Bis-WT DM mice compared to Bis-WT mice in the kidneys. In contrast, there was a significant decrease in Bis expression in Bis-HT DM mice compared to Bis-WT DM mice even under the same degree of hyperglycemia. Serum creatinine and albuminuria were increased in the Bis-HT DM mice compared to those of Bis-WT DM mice. More glomerular matrix expansion, TGF-1 and HIF-1 expression, and tubulointersitial fibrosis were also noted in the Bis-HT DM mice related to increases in apoptotic glomerular and tubular epithelial cells, accompanying with decreases in Bis and Bcl-2 expressions. SOD1 and SOD2 expressions were significantly decreased in the Bis-HT DM mice compared to those of Bis-WT DM mice, suggesting increased oxidative stress. Interestingly, even under the established diabetic nephropathy, anti-oxidant tempol treatment reversed renal damages in the Bis-HT DM mice associated with increasing Bis and Bcl-2 expressions and decreasing oxidative stress.

Conclusion: Our results demonstrate that Bis protein has a protective effect on diabetic nephropathy and that its effect may be explained, at least in part, by preserving of anti-oxidative function.

Key Words: 당뇨병성 신병증, 산화 스트레스, 세포자멸사
Bis, Diabetic nephropathy, Oxidative stress