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Streptozotocin으로 유발된 당뇨병 쥐에서 Bis 단백 결손이 당뇨병성 신증을 악화시키는 기전에 대한 연구

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Role of Bis on the Development and Progression of Diabetic Nephropathy in Streptozotocin-Induced Type 1 Diabetes

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Introduction : Bis gene, which acts as the BCL interacting death suppressor gene, has been identified as encoding a Bcl-2 binding protein. Bis is ubiquitous expression in the cytoplasm on the cells, and has anti-oxidative and anti-apoptotic activity by enhancing Bcl-2 activity in a synergistic manner against Bax- and Fas-mediated cell death. Recently, we have demonstrated that homozygous Bis-/- mice showed the serious metabolic deterioration such as hypoglycemia and lipid accumulation in the liver resulting in early lethality associated with oxidative stress. In this study, we investigated the role of Bis on the development and progression of diabetic nephropathy using hetero mice deficient in Bis.

Methods : Male Bis deficient Hetero (+/-; Bis-H) mice and normal Bis wild-type (+/+; Bis-WT) at 8 wks of age treated with or without low-dose streptozotocin for 5 days were divided into 4 groups.

Results : After 20 weeks of diabetes, fasting blood glucose and HbA1C were not significant different between diabetic Bis-H and Bis-WT mice. In the kidney, Bis was mainly expressed in the proximal tubule, thick ascending loop of Henle, and collecting tubule. In diabetic Bis-H mice, 24 hr urinary albumin excretion was 3-fold increased compared with that of the diabetic Bis-WT. In contrary to the increased expression of Bis in the kidney in diabetic Bis-WT mice, there was no increase in diabetic Bis-H mice. Renal histology demonstrated that more glomerular expansion, TGFbeta expression, and inflammation were noted in diabetic Bis-H mice compared with those of diabetic Bis-WT mice. Moreover, tubulointerstitial fibrosis in diabetic Bis-H mice was more prominent with relation to the increases in apoptotic tubular epithelial cells. Interestingly, real-time RCR demonstrated that Bcl-2, SOD1 and SOD2 mRNA were significantly decreased in diabetic BIS-H mice compared with those of diabetic BIS-WT mice. There was no difference in Bax mRNA between the diabetic BIS-WT and BIS-H mice. Urinary 8-isoprostane and 8-OH-deoxyguanosine levels were also significantly increased in diabetic Bis-H mice compared with those of diabetic Bis-WT mice. These changes were not observed in nondiabetic Bis-H and Bis-WT.

Conclusion : Our results show that the deficinecy of Bis has considerable influences on the development and progression of diabetic nephropathy, especially tubulointersitial atrophy and fibrosis, with relation to the oxidative stress in streptozotocin-induced type 1 diabetes.

Key Words : 당뇨병, 신증, 산화스트레스
Bis, Diabetes, Oxidative stress