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Bis-Haploinsufficiency Aggravates Diabetic Nephropathy by Increasing Oxidative Stress

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Introduction: Bcl-2 interacting cell death suppressor (Bis) is ubiquitously expressed in various tissues and exhibits anti-stress and anti-apoptotic activity. Recently, it has been shown that suppression of Bis expression causes cells to become more susceptible to oxidative stress. Notably, oxidative stress has been implicated in the pathogenesis of diabetic nephropathy. In this study, we investigate the potential role of Bis as an antioxidant protein in diabetic nephropathy.

Methods: Diabetic nephropathy was induced by the injection of streptozotocin in heterozygote mice for bis gene (Bis-HT) and compared the resulting phenotypes with wild type (Bis-WT) mice up to 20 weeks after diabetes induction. An antioxidant tempol was administered for 8 weeks, starting after 12 weeks of diabetes induction.

Results: Renal injuries represented by decrease in plasma creatinine and increase in albuminuria were aggravated in diabetic Bis-HT (Bis-HT DM) mice compared to diabetic Bis-WT (Bis-WT DM) mice, accompanied with the marked increase in the oxidative stress markers such as urinary isopsortane, urinary 8-hydroxy-deoxyguanosine (8-OH-dG) as well as serum 8-OH-dG. Moreover, the glomerular matrix expansion, TGF-β1 and HIF-1α expression, and tubulointerstitial fibrosis were also notably increased in the Bis-HT DM mice than Bis-WT DM mice with the same degree of hyperglycemia. In addition, the proportion of apoptotic glomerular and tubular epithelial cells in Bis-HT DM mice was increased in Bis-HT DM mice than in Bis-WT DM mice. These severe outcomes of diabetic nephropathy, renal functions as well as histological changes, were all restored by tempol treatment, indicating the impairment of antioxidant system in Bis-HT DM mice. The expression of SOD1 and SOD2 was increased by DM induction in Bis-WT mice, correlating with total SOD activities, which was not observed in Bis-HT and Bis-HT DM mice. In addition, in vitro study showed that the knock down of Bis expression also resulted in the failure of induction of SOD activity in HK-2 and NMS cells and induction or maintenance of SOD1 expression was more affected by Bis suppression than SOD2 expression.

Conclusion: Our results suggest that decreased antioxidant capacity of Bis may aggravate DN in Bis-HT DM mice, which could possibly result from disruption in the regulation of SOD1 or SOD2 protein quality upon oxidative stress.

Key Words: 당뇨병성 신증, 산화스트레스, 항산화제
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