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실험적 당뇨병성 신병증 모델에서 사구체 비후 및 세포 사멸에 미치는 Klotho의 효과

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남보영, 이순하, 강혜영, 팽지선, 김성훈, 이미정, 신동호, 오형중, 박정탁, 유태현, 강신욱, 한승혁

Restoration of Klotho Ameliorates Glomerular Hypertrophy and Apoptosis in Diabetic Nephropathy

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Background: Klotho, a known co-receptor for FGF23, has been demonstrated to have a protective role in experimental acute tubule-interstitial injury. However, the effects of klotho on glomeruli are largely unknown in diabetic conditions. Therefore, we aimed to investigate the role of glomerular klotho in diabetic nephropathy (DMN).
Methods: Mouse mesangial cells (MMC) and podocytes were treated with either normal glucose (5.6 mM, NG), high glucose (30 mM, HG) or NG+mannitol (24.4 mM, NG+M). Mice were injected either with diluents (n=16, C) or with streptozotocin (50 mg/kg) intraperitoneally (n=16, DM) to induce diabetes. Eight mice from each group were treated daily with 10 ug/kg recombinant klotho (rKL) using osmotic minipumps. Kidneys were collected after 8 weeks.
Results: The expressions of klotho mRNA and protein were down-regulated in MMC and podocytes with HG treatment compared to NG or NG+M cells. In parallel, the expressions of p21Cip1, p27Kip1, cleaved caspase-3, and the ratio of Bax/Bcl-2 were significantly increased in HG-treated MMC and podocytes compared to NG or NG+M cells. When MMC and podocytes were treated with rKL, HG-induced p21Cip1, p27Kip1, cleaved caspase-3, and Bax protein expressions were significantly attenuated. In addition, knock down of klotho with siRNA transfection further increased the expression levels of these hypertrophy- and apoptosis- related proteins. In vivo, the expression of klotho was significantly decreased in DM glomeruli compared to C glomeruli at 8 weeks of diabetes. The protein expressions of p21Cip1, p27Kip1, cleaved caspase-3, and the ratio of Bax/Bcl-2 were significantly increased in glomeruli from DM compared to C mice. Treatment with rKL via osmotic minipumps significantly ameliorated the glomerular protein expressions of p21Cip1, p27Kip1, cleaved caspase-3, and Bax in DM compared to DM mice treated with diluent alone.
Conclusion: Decreased klotho contributed to the development of cellular hypertrophy and apoptosis in MMC and podocytes under diabetic conditions. Present study revealed that restoration of klotho might be a potential therapeutic target in DMN.

Key Words: klotho, 족세포, 당뇨병성 신병증
klotho, Podocyte, Diabetic nephropathy