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A New Strategy for the Treatment of Salt Sensitive Hypertension: Targeting for Normalization of Autophagy in the Renal Tubular Cells by an Antiaging Protein, SIRT1

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Summary

The kidney is a typical target organ of age-associated tissue damage, and the increased incidence of chronic kidney disease in the elderly is a health problem worldwide. However, there is little or no information on the mechanisms underlying age-associated kidney damage. Aging is also one of the important determinants of salt sensitivity of blood pressure. Thus, studies designed to determine the mechanisms on the aging could help formulate interventions that delay the onset and/or progression of CKD and reduce the salt sensitivity of blood pressure in elderly patients. Caloric restriction (CR) significantly inhibited age-associated increases in the renal dysfunction marker serum cystatin C, 24-hour urinary albumin excretion, and fibrotic changes in glomerular and interstitial lesions, with significantly reduced urinary excretion of the oxidative stress marker 8-OHdG. EM analysis showed accumulation of senescent mitochondria in PTCs of ad libitum-fed (AL) mice, which exhibited swelling and disintegration of cristae. In contrast to PTCs of AL mice, those of CR mice showed normal mitochondrial morphology with numerous auto (lyso) phagosomes. Sirt1 activity was decreased in the aged kidney and enhanced by long-term CR. Furthermore, Sirt1 mRNA expression levels correlated negatively with serum cystatin C levels and prevalence of D-17, which suggests that Sirt1 is associated with age-associated kidney dysfunction. Sirt1^{+/-} AL mice showed damaged mitochondria, higher levels of urinary 8-OHdG excretion, and higher prevalence of point mutation of mtDNA in the kidney; additionally, CR failed to suppress these abnormalities. These results suggest that Sirt1 in the kidney is essential for the CR-mediated enhancement of hypoxia-associated mitochondria oxidative damage *in vivo*. The present study demonstrated that mitochondrial damage in aged kidney is associated with Sirt1 deficiency and that Sirt1 promotes cell adaptation to hypoxia through autophagy in aged kidney.