Abstract

Background/aims: Inhibition of glucose influx into proximal tubular cells (PTCs) by sodium-glucose co-transporter 2 (SGLT2) inhibitors revealed prominent therapeutic impacts on diabetic kidney disease (DKD). Collectrin (CLTRN) serves as a chaperone for the trafficking of neutral amino acid transporters in the apical membranes of proximal tubular cells. We investigated the beneficial effects of reduced influx of amino acids into proximal tubular cells in diabetes and obesity model of Cltrn-/y mice.

Methods: Cltrn+/y and Cltrn-/y mice at 5 weeks of age were assigned to standard diet- (STD) and streptozotocin and high fat diet-treated (STZ-HFD) groups.

Results: At 22-23 weeks of age, body weight and HbA1c levels significantly increased in STZ-HFD-Cltrn+/y compared to STD-Cltrn+/y; however, they were not altered in STZ-HFD-Cltrn-/y compared to STZ-HFD-Cltrn+/y. At 20 weeks of age, urinary albumin creatinine ratio (UACR) was significantly reduced in STZ-HFD-Cltrn-/y compared to STZ-HFD-Cltrn+/y. Under the treatments with STZ and HFD, the *Cltrn* gene deficiency caused significant increase in urinary concentration of amino acids such as Gln, His, Gly, Thr, Tyr, Val, Trp, Phe, Ile, Leu and Pro. In proximal tubular cells in STZ-HFD-Cltrn+/y, the enlarged lysosomes with diameter of 10 μm or more were associated with reduced autolysosomes, and the formation of giant lysosomes was prominently suppressed in STZ-HFD-Cltrn-/y. Phospho-mTOR and inactive form of phospho-TFEB were reduced in STZ-HFD-Cltrn-/y compared to STZ-HFD-Cltrn+/y.

Conclusions: The reduction of amino acids influx into proximal tubular cells inactivated mTOR, activated TFEB, improved lysosome function, and ameliorated vacuolar formation of PTCs in STZ-HFD-Cltrn-/y mice.