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α-galactosidase A 결핍 생쥐에서 AQP2와 UT-B의 발현 변화

이화여자대학교 해부학교실[1], 이화여자대학교 생화학교실[2], 경북대학교 생화학교실[3]

김지은[1], 이수연[1], 이세진[1], 권태환[3], 정성철[2], 한기환[1]

Abnormal Expression of AQP2 and UT-B Causes Urine Concentration Defect in α-galactosidase A Deficient Mice

Ji-Eun Kim[1], Su-Youn Lee[1], Sae-Jin Lee[1], Tae-Hwan Kwon[3], Sung-Chul Jung[2], Ki-Hwan Han[1]

Department of Anatomy[1] Ewha Womans University
Department of Biochemistry[2] Ewha Womans University
Department of Biochemistry[3] Kyungpook National University

Fabry disease is an inherited disorder caused by deficiency of α-galactosidase A (α-Gal A) resulting in lysosomal accumulation of globotriaosylceramide (Gb3). The purpose of this study was to investigate the mechanism of the decreased urinary concentration, one of the most important renal manifestation of Fabry disease, in α-Gal A deficient mice.

Kidney tissues were processed for α-Gal A enzyme activity assay, Gb3 level quantification, immunocytochemistry, immunoblot analysis, and primary cell culture.

α-Gal A deficiency caused typical histopathology and significant polyuria that was associated with increased renal Gb3 level. Fabry kidneys showed a significantly increased the expression of ER stress proteins, Bip and CHOP. Immunocytochemistry revealed that the expression of Bip and CHOP was induced mainly in glomeruli, outer medullary vascular bundles, and medullary collecting duct. CHOP immunoreactivity was also detected in the descending thin limb (DTL) of the loop of Henle. UT-B, AQP2, and AQP1 are key transport proteins involved in urine concentration in vascular bundles, collecting duct, and DTL, respectively. Expression of UT-B and AQP2 proteins significantly decreased in Fabry kidneys, but the abundance of AQP1 protein remained unchanged. Confocal microscopy demonstrated that AQP2 and UT-B were abnormally distributed in the cytoplasm in Bip- and CHOP-expressing vascular bundles and medullary collecting ducts. However, both AQP-2 and UT-B were mainly localized in the LAMP-1-positive endosomes and lysosomes, but not in the ER. We also demonstrated that Gb3 treatment on primary cultured medullary collecting duct cells decreased the expression of AQP2. Enzyme replacement therapy improved urine concentration ability and recovered AQP2 and UT-B protein expression. These findings suggest that alteration of AQP2 and UT-B expression may play an important role in the urinary concentration defect and recovery after enzyme therapy in Fabry disease.
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Fabry disease, Collecting duct, AQP-2