Restoring autophagy to protect the kidney: A novel mechanism of SGLT2 inhibitors

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to slow the progression of chronic kidney disease (CKD) regardless of diabetes status and to reduce the incidence of acute kidney injury (AKI). However, the underlying renoprotective mechanisms remain incompletely understood, particularly regarding the role of autophagy, an intracellular degradation system. Glomerular hyperfiltration increases albumin exposure to proximal tubules, leading to autophagy impairment. In this study, we focused on the SGLT2 inhibitor empagliflozin (EMPA) and examined its effects using a low-proteinuric obese mouse model. EMPA alleviated glomerular hyperfiltration, reduced tubular albumin exposure, and restored autophagy. Furthermore, in a renal ischemia–reperfusion injury model, EMPA improved autophagy activity and attenuated AKI. These findings suggest that EMPA confers kidney protection by reducing lysosomal stress and restoring autophagy, providing new mechanistic insight into the renoprotective actions of SGLT2 inhibitors (Figure 1).

Background & Results

SGLT2 inhibitors are emerging as key agents that protect against CKD progression and reduce AKI risk, yet the precise mechanisms remain unclear. Because glomerular hyperfiltration–induced albumin overload disrupts autophagy in proximal tubules, we investigated the effects of empagliflozin (EMPA) on the autophagy–lysosome system. In obese mice fed a high-fat diet, EMPA ameliorated glomerular hyperfiltration and prevented the formation of vacuolar lesions in proximal tubules. These vacuoles were positive for the lysosomal marker LAMP1 and toluidine blue, indicating lysosomal phospholipid accumulation that was relieved by EMPA (Figure 2).

Using proximal tubule–specific megalin knockout mice, we confirmed that EMPA reduced albumin reabsorption in obese kidneys. Moreover, analyses in GFP-LC3 transgenic mice demonstrated that EMPA restored autophagic flux impaired by obesity. In a renal ischemia–reperfusion model, EMPA improved autophagy and mitigated AKI severity. However, in proximal tubule–specific Atg5-deficient mice, these protective effects were abolished, confirming that EMPA's renoprotection depends on functional autophagy.

Significance of the research and Future perspective

While pharmacological modulation of autophagy has been attempted in various diseases, indiscriminate activation may overload lysosomes and limit therapeutic efficacy. Our findings demonstrate that EMPA exerts kidney protection by reducing lysosomal burden and appropriately restoring autophagy. This mechanism highlights a novel therapeutic axis involving megalin, autophagy, and lysosomes. Modulation of this pathway may represent a common strategy for treating kidney injury associated with obesity, diabetes, and aging. Future studies should explore how EMPA-mediated lysosomal correction enhances kidney resilience across diverse pathological contexts, potentially leading to new approaches for preventing CKD progression and AKI.

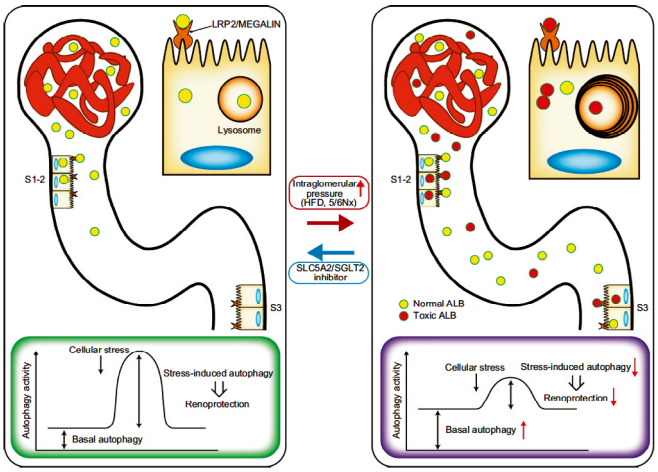

Figure1

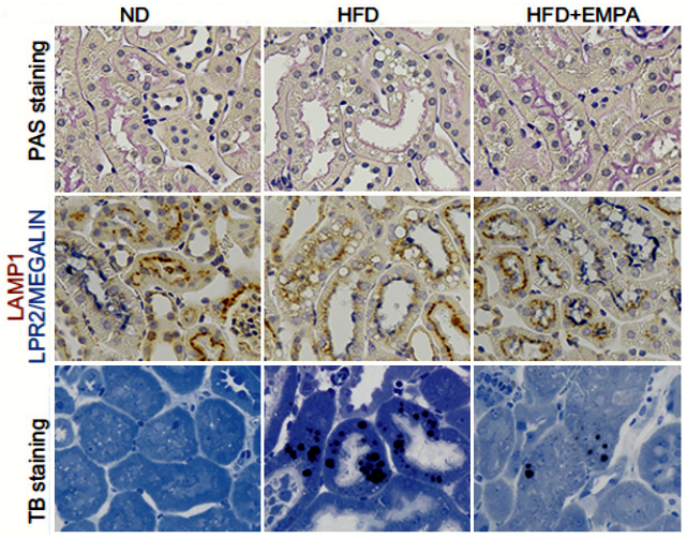

Figure2

Patent

Treatise Matsui, Sho; Yamamoto, Takeshi; Isaka, Yoshitaka et al. Empagliflozin protects the kidney by reducing toxic ALB (albumin) exposure and preventing autophagic stagnation in proximal tubules. Autophagy. 2025, 21, 583-597. doi: 10.1080/15548627.2024.2410621
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Keyword SGLT2 inhibitors, autophagy, obesity, chronic kidney disease (CKD), acute kidney injury (AKI)