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5-lipoxygenase inhibition ameliorates diabetic kidney disease by attenuating renal tubular epithelial cell ferroptosis

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Objectives : The enzyme 5-lipoxygenase(5-LOX) plays a crucial role in the conversion of arachidonic acid into 5-hydroperoxyeicosatetraenoic acid and leukotrienes, known mediators contributing to diverse pathological inflammatory responses. Additionally, 5-LOX serves as a major source of reactive oxygen species (ROS), which can lead to lipid peroxidation and subsequent ferroptosis. The aim of study is to investigate the pathophysiological implications of 5-LOX in diabetic kidney disease (DKD).
Methods : In vitro experiments utilized HKC-8 cells, a human-derived renal proximal tubular cell line. Diabetes induction in male C57BL/6J mice was achieved through streptozotocin injection. Zileuton was used to inhibit 5-LOX activity.
Results : Under high glucose conditions, the expression of 5-LOX was significantly increased in both HKC-8 cells and kidney tissues. The overexpression of 5-LOX was associated with aggravated hyperglycemia-induced expressions of profibrotic cytokines and ROS formation. Conversely, the knockdown of 5-LOX mitigated these deleterious effects. Interestingly, hyperglycemic stimuli led to a reduction in glutathione peroxidase 4 (GPX4) expression and increases in Acyl-CoA synthetase long chain family member 4 (ACSL4), ferritin heavy chain 1 (FTH-1), and malondialdehyde (MDA) expressions, indicating activation of pro-ferroptotic signals. Overexpression of 5-LOX under high glucose conditions induced significant tubular cell ferroptosis, a phenomenon rescued by ferrostatin-1 or Zileuton treatment. Finally, streptozotocin-induced hyperglycemic mice exhibited decreased kidney function and worse interstitial fibrosis, accompanied by lower GPX4 and higher ACSL4 and FTH-1 levels compared to normoglycemic mice. Administration of Zileuton significantly restored these hyperglycemia-associated deleterious alterations.
Conclusions : These findings demonstrate the pivotal role of 5-LOX in intracellular ROS generation and consequent tubular cell ferroptosis under sustained hyperglycemic conditions. Inhibition of 5-LOX not only ameliorates ferroptotic renal tubular cell death but also mitigates diabetes-induced loss of kidney function. This suggests that 5-LOX could be a potential target for novel treatment option of DKD.