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Administration of 2-mercaptoethanol prevents oxidative stress and inflammation during unilateral ureteral obstruction

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Objectives:

Ferroptosis as an iron-dependent mode of regulated cell death is triggered by disturbed redox homeostasis and lipid peroxidation through overloaded iron. However, the role of ferroptosis in renal fibrosis remains to be defined.

Methods: Unilateral ureteral obstruction (UUO) or sham-operation in left kidneys of female C57BL/6 mice aged 11-14 weeks was carried out. Twenty-four hours before UUO or sham-operation, mice were intraperitoneally and daily treated with 2-mercaptoethanol (a cyst(e)ine transport promotor; 3, 10, or 30 mg/kg body weight per day) or 0.9% saline (vehicle). Levels of SLC7A11, glutathione peroxidase 4 (GPX4), copper/zinc superoxide dismutase (CuZnSOD), manganese superoxide dismutase (MnSOD), connective tissue growth factor (CTGF), α -smooth muscle actin (α -SMA), interleukin-6 (IL-6), and intercellular adhesion molecule-1 (ICAM-1) expressions were measured by western blot analysis.

Results: UUO decreased the expression of SLC7A11, a known ferroptosis-related glutamate/cystine transporter, whereas exogenous 2-mercaptoethanol significantly suppressed UUO-induced decrease of SLC7A11 expression. During UUO, ferroptosis-related GPX4 and other antioxidant enzymes including CuZnSOD and MnSOD were downregulated, but 2-mercaptoethanol markedly reduced their downregulations at 10 days after UUO. Furthermore, expressions of ICAM-1 and IL-6 among pro-inflammatory proteins were increased during UUO, but exogenous 2-mercaptoethanol significantly reduced their increases at 10 days after UUO. However, UUO-induced upregulation of profibrotic proteins including α -SMA and CTGF in kidneys was not significantly altered by any dose of 2-mercaptoethanol.

Conclusions:

These data suggest that a pharmacological inhibition through promoting SLC7A11 glutamate/cystine transporter protects kidneys against oxidative stress and inflammation during unilateral ureteral obstruction. (NRF-2016R1C1B2012080)