Effects of hypoxia inducible factor alpha prolyl hydroxylase inhibitor on the development of renal fibrosis in mouse unilateral ureteral obstruction model.

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Orally active hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors that stabilize HIF protein and stimulate the production of erythropoietin in clinical trials to treat renal anemia. We have shown that HIF-1 dependent gene expression of profibrogenic molecules, PAI-1 and CTGF was observed in mouse unilateral ureteral obstruction (UUO), an animal model of renal fibrosis (Kabei et al. J Pharmacol Sci. 2018). Present study was conducted to examine the effects of FG-4592, a prolyl hydroxylase inhibitor on the development of renal fibrosis. Male C57BL/6J mice orally given either FG-4592 (50 mg/kg/day) or vehicle were subjected to UUO. At 3 days after UUO, FG-4592 potentiated the increased mRNA expression of PAI-1 and CTGF in the obstructed kidneys but such potentiation disappeared at 7 days after UUO. FG-4592 did not affect the increased mRNA expression of collagen I, collagen III and TGF beta1 observed in the obstructed kidneys. Renal cortical collagen III positive stained area were not affected by FG-4592 either at 3days or 7 days after UUO. It is suggested that FG-4592 had little effects on renal fibrosis even though high dose of FG-4592 used in the present study transiently potentiated gene expression of PAI-1 and CTGF in the UUO kidney.