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DIZE (Diminazene aceturate) exacerbates renal fibrosis after unilateral ureteral obstruction in mice

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Objectives: Diminazene aceturate (DIZE) has been used for the treatment of animal trypanosomiasis and DIZE is also well known as angiotensin-converting enzyme 2 activator (ACE2) which converts angiotensin II to angiotensin 1-7. In recent studies, it has been suggested that DIZE has anti-inflammatory and anti-fibrotic activities in many human chronic disease models. However, the role of DIZE in kidney fibrosis remains unclear. So, we investigated the role of DIZE in the progression of renal fibrosis after unilateral ureteral obstruction (UUO), one of the most popular models of chronic kidney disease (CKD), in mice.

Methods: C57BL/6 female mice were divided into two groups of 6 each: vehicle (saline) treatment UUO group and 15 mg/kg DIZE daily treatment UUO group. Before UUO, mice were anesthetized by 50 mg/kg body weight pentobarbital, and after anesthesia induction, UUO surgery was operated by ligating the ureter of the right kidney with 6–0 silk. On the seventh day following the UUO surgery, kidneys were collected for analysis of renal fibrosis (α-smooth muscle actin expression, Masson's trichrome staining, TGF-β/p-SMAD3), inflammation (pro-inflammatory cytokine and chemokine synthesis as well as neutrophil and macrophage infiltrations), and apoptosis/necrotic cell death (TUNEL positive renal tubular cells and PAS staining) were analyzed.

Results: To our surprise, we show here that treatment of DIZE exacerbates renal fibrosis by activating profibrotic and proinflammatory signal pathways and apoptotic/necrotic cell death in the obstructed kidneys.

Conclusions: These data suggest that DIZE aggravates kidney fibrosis in a different way from other DIZE-mediated anti-fibrotic effects shown in other organs. In the future study, we will investigate the signal pathway of DIZE-mediated pro-fibrotic activity in the kidney such as M2 macrophage or ACE2 activation.