Beneficial Effects of Relaxin in an *In Vivo* Experimental Model of Ischemic Acute Kidney Injury

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Since its discovery in 1926, relaxin (RLX) has long been regarded as a peptide hormone of ovarian origin involved in the periparturient widening of the pubic symphysis. More recently, growing evidence have suggested that RLX exerts a broad range of other biological effects on many organs and apparatus, including the cardiovascular system (Bani D. et al., 2011). Clinical trials studying intravenous recombinant human H2 RLX (rhRLX) as a treatment for patients hospitalized with acute heart failure have recently shown significant improvement in clinical outcomes without any major adverse events. Although several studies have demonstrated that RLX ameliorates impaired renal function by exerting antifibrotic and regenerative effects (Samuel CS. et al., 2006), its role in renal ischemia/reperfusion (I/R) injury, one of the most common pathophysiological event leading to acute kidney injury (AKI), has never been tested. Using a well-known rat model of 1h bilateral renal artery occlusion followed by 6 h reperfusion (Collino M. et al., 2005), we investigated the effects of rhRLX(5 μg /Kg i.v.) given both at the beginning and after 3 h reperfusion. Serum and urinary indicators of renal injury and dysfunction (serum urea and creatinine, creatinine clearance and urinary excretion of N-acetyl-β-glucosaminidase) were measured. Administration of the exogenous rhRLX attenuated all markers of renal injury and dysfunction caused by I/R. Simultaneously, rhRLX evoked a significant reduction in local neutrophil infiltration, measured as myeloperoxidase activity and intercellular-adhesion- molecule-1 expression, as well as in tissue oxidative stress, measured as levels of thiobarbituric reactive substances and 8-hydroxydeoxy-guanosine and expression/activity of the endogenous antioxidant enzymes Mn- and Cu/Zn- superoxide dismutases. Interestingly, the reduced oxidative stress status and neutrophil activation were associated with RLX-induced activation of endothelial nitric oxide synthase and up-regulation of inducible nitric oxide synthase, possibly secondary to activation of Akt and ERK1/2, respectively. Moreover, rhRLX protects the kidney against I/R injury by a mechanism that involve changes in nitric oxide (NO) signaling pathway. Overall, these findings provide further evidence to the concept that RLX may be regarded as a pharmacological tool in diseases characterized pathogenically by vascular dysfunction and impaired NO production, such as cardiovascular ischemic diseases, including AKI.

Bani D. et al., (2011) *Curr Drug Saf*. 6, 324-328.
Samuel CS. et al., (2006) *Kidney Int*. 69, 1498-1502.
Collino M. et al., (2005) *Kidney Int*. 68, 529-536.