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Acute treatment with relaxin attenuates the injury/dysfunction induced by renal ischemia/reperfusion injury

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Summary

Although preclinical and clinical studies have demonstrated that relaxin (RLX) ameliorates impaired renal function by exerting antifibrotic and regenerative effects, its role in renal ischemia/reperfusion (I/R) injury has never been investigated. Using a well-known rat model of 1h bilateral renal artery occlusion followed by 6 h reperfusion, we investigated the effects of human recombinant RLX (5 μg /Kg e.v.) given both at the beginning and after 3 h reperfusion. Serum and urinary indicators of renal injury and dysfunction were measured. Interestingly, administration of the exogenous RLX attenuated all markers of renal injury and dysfunction caused by I/R. Overall, we document here, for the first time, that RLX protects against I/R-induced renal injury and dysfunction. The results of this study offer good perspectives for the clinical potential of RLX in the medical treatment of renal diseases.

Key words

Relaxin, ischemia/reperfusion, kidney, inflammation, oxidative stress

Although initially perceived as being merely a peptide hormone of ovarian origin involved in the periparturient widening of the pubic symphysis, relaxin (RLX) has been later shown to exert a broad range of biological effects on many organs and apparatus, including the cardiovascular system (Bani et al., 2011). We and others have shown that RLX affords a clear-cut protection against ischemia/reperfusion (I/R) injury in the heart, brain, intestine and lung (Bani et al., 1998; Masini et al., 2006; Alexiou et al., 2010). Both RLX and its main receptor, named relaxin family peptide receptor 1 (RXFP1), are expressed in both the human and rodent kidney and growing evidence demonstrates that RLX exerts relevant antifibrotic and regenerative effects in several experimental models of renal fibrosis (Samuel et al., Curr Opin 2009). However, to the best of our knowledge, there is no information on the role of RLX in renal I/R injury, which is one of the most common patophysiological event leading to acute kidney injury (AKI), a life-threatening condition associated with high morbidity and mortality. Thus, we have investigated the effects of RLX administration on the recovery of renal function following I/R injury. Anesthetized

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male Wistar rats rats were subjected to bilateral renal occlusion for 1h using non-traumatic artery clamps to clamp the renal pedicles, followed by reperfusion for 6h. Sham-operated rats underwent surgical procedures identical to those used for I/R except that artery clamps were not applied. At the end of the reperfusion, the anesthetized rats were killed by aortic exsanguinations and the kidneys were isolated, weighed, and rapidly freeze-clamped and stored at −80 °C. Animal care was in compliance with Italian regulations on the protection of animals used for experimental and other scientific purposes (D.M. 116/92). The experimental protocol, approved by the Turin University Ethics Committee, was performed as described elsewhere (Collino et al., 2011). A group of rats received human recombinant RLX (5 μg /Kg e.v.) both at the beginning and after 3 h reperfusion. When compared to sham-operated rats, rats that underwent I/R exhibited a significant increase in serum creatinine and urea and attenuation in creatinine clearance (CCL) and urine flow, thus indicating renal dysfunction and reperfusion injury (Table 1). Tubular injury is suggested by a significant increase in urinary excretion of N-Acetyl-β-glucosaminidase (NAG), a well-known marker of tubular cell dysfunction. Compared to rats subjected to I/R only, therapeutic administration of RLX during reperfusion significantly attenuated both glomerular and tubular dysfunction caused by renal I/R, as shown by statistically significant modification in levels of serum creatinine, serum urea, CCL, urine flow and urinary NAG excretion (Table 1). Overall, the results of this study are the first to directly demonstrate the beneficial effects of acute RLX administration during renal I/R injury, thus suggesting a new potential therapeutic approach for the treatment of AKI.

Table 1. Effects of acute RLX administration on the renal dysfunction and injury caused by I/R in male Wistar rats.

	Sham (n = 8)	**I/R (n = 8)**	**I/R+RLX (n = 8)**
Serum Urea, mg/dL	13.32±1.84*	44.32±6.18	23.58±3.64*
Serum Creatinine, mg/dL	1.12±0.07*	2.55±0.26	1.75±0.11*
Creatinine Clearance, mL/min	0.056±0.004*	0.007±0.004	0.021±0.002*
Urinary flow, mL/min/100 g bw	0.0076±0.001*	0.0044±0.0008	0.0091±0.0007*
Urinary NAG, IU/L	20.20±2.44*	56.34±7.87	28.87±4.21*

Data are means±S.D. * p< 0.01 vs I/R

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