SP180

EFFECT OF JNK INHIBITOR IN A RAT MODEL OF RENAL ISCHEMIA-REPERFUSION INJURY

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Introduction

+ The pathophysiology of ischemic acute kidney injury is very complex and still not completely understood.
+ Experimental models of renal ischemia reperfusion (IR) injury in rodents are widely used to study the effect of therapeutic and preventing strategies.
+ Previous studies demonstrated that the blockade of c-Jun N-terminal kinase (JNK) signaling pathway can prevent acute tubular necrosis and renal dysfunction induced by IR injury[1].

Objective

The aim of our study was to evaluate the effect of JNK inhibitor (XG-102) on kidney function and histological lesions induced by bilateral kidney IR injury in rats.

Methods

+ **Animals:** rat, Sprague-Dawley, males (9-12/group).
+ **Surgery:** bilateral kidney IR injury by clamping of renal pedicles.
+ **Study design:**

Protocol #	Ischemia	Reperfusion	XG-102 administration	
			Dose (mg/kg)	Timing
Protocol 1	40 min	24 h	2	20 min after IR
Protocol 2	40 min	48 h	8	1 h before IR
Protocol 3	40 min	72 h	8	24 h after IR

+ **Experimental groups:**

Group	IR	Treatment (*i.v*)
Sham	no	vehicle
IR	yes	vehicle
IR+XG-102	yes	XG-102

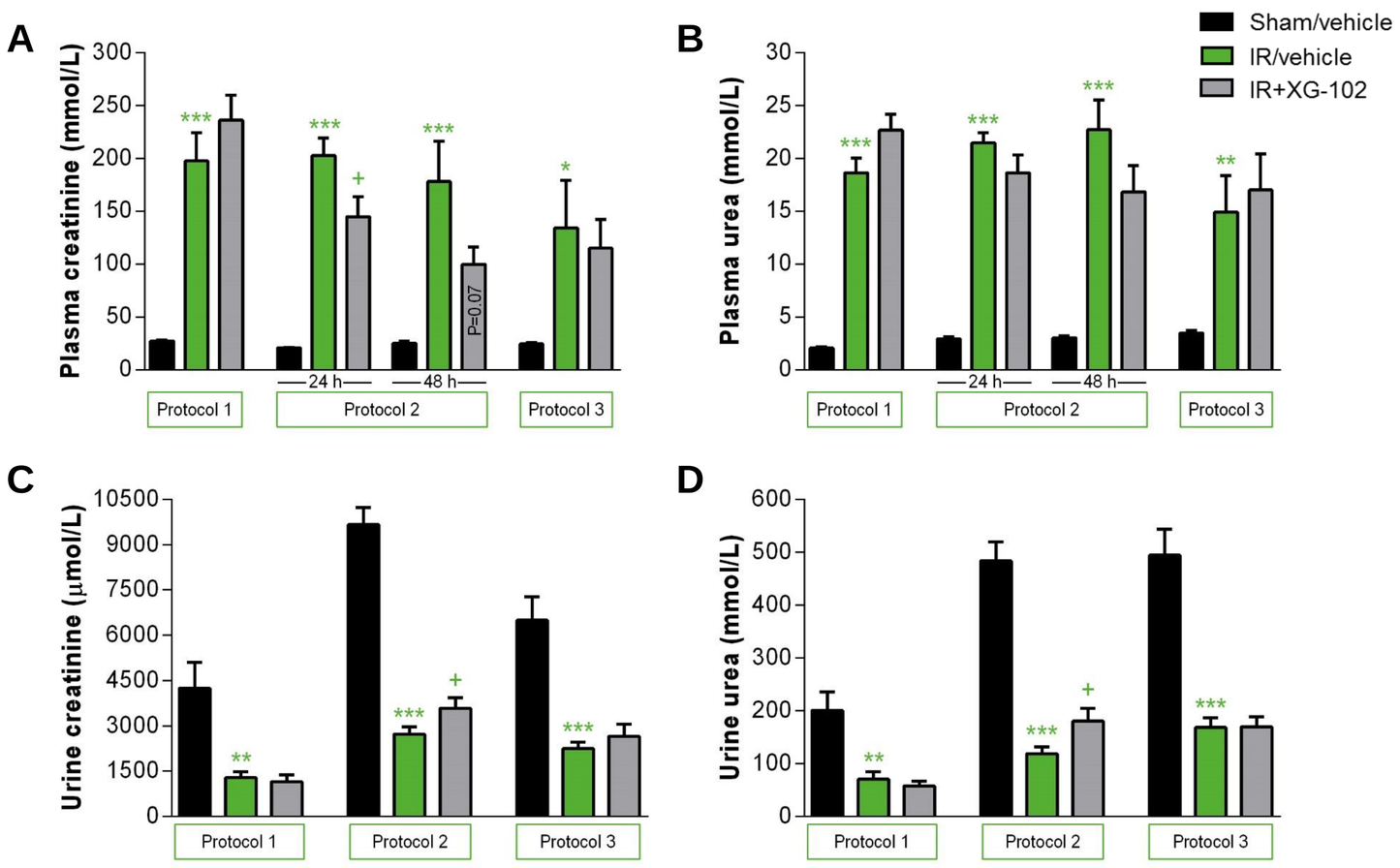
For each protocol:
+ Sham animals underwent the same surgery w/o clamping of kidney pedicles.
+ XG-102 or its vehicle (NaCl 0.9%) were administered into the tail vein.
+ 9-12 animals per group

+ **Kidney function biomarkers:** creatinine and urea using ABX Pentra 400 clinical chemical analyser.
+ **Histology:** tubular damages evaluation by score system on hematoxyline/eosin (HE) staining of kidney sections.

Conclusions

Results

Effect of XG-102 on kidney function biomarkers

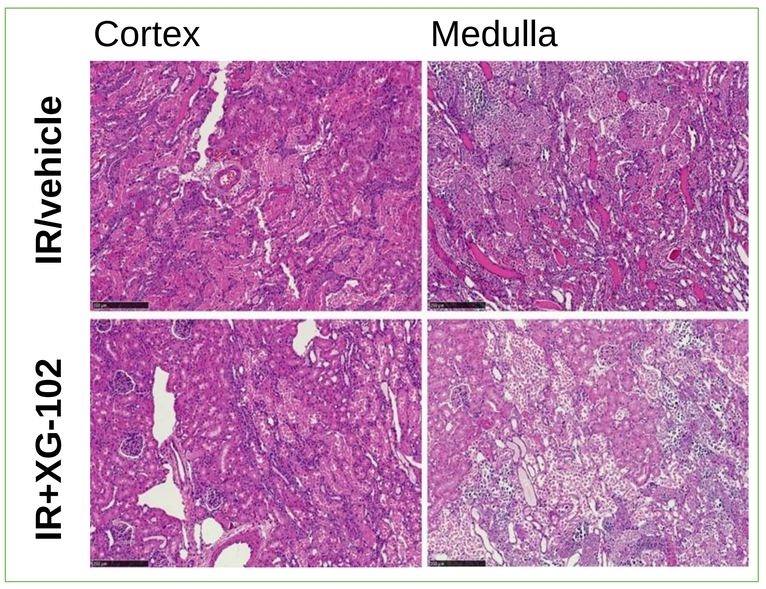


Values represent mean ± SEM (n=9-12/group)
*P<0.05; **P<0.01;***P<0.001 *vs* Sham/vehicle. +P<0.05 *vs* IR/vehicle (unpaired *t*-test w or w/o Welch's correction)

+ In male SD rats, bilateral kidney IR induced:
  + a significant increase of plasmatic creatinine (**A**) and urea (**B**);
  + a significant decrease of urinary creatinine (**C**) and urea (**D**).
+ XG-102 administered 1 hour before ischemia (**Protocol 2**) significantly reduced plasma creatinine and increased creatinine and urea excretion.
+ No significant effect was observed in protocol 1 and 3.

Effect of XG-102 on tubular damages

A



B

Protocol #	Surgery and Treatment		Tubular changes			Total Tubular score
			Tubular degeneration/ necrosis	Tubular cast	Basophilic tubules	
Protocol 1	Sham/vehicle	**mean**	**0.00**	**0.00**	**0.25**	**0.25**
		±SEM	0.00	0.00	0.13	0.13
	IR/vehicle	**mean**	**3.45** ***	**3.00** ***	**1.36** ***	**7.82** ***
		±SEM	0.16	0.00	0.20	0.30
	IR/XG-102	**mean**	**2.67** +	**2.50** +	**1.33**	**6.50** +
		±SEM	0.19	0.15	0.19	0.23
Protocol 2	Sham/vehicle	**mean**	**0.00**	**0.00**	**0.18**	**0.18**
		SEM	0.00	0.00	0.12	0.12
	IR/vehicle	**mean**	**3,00** ***	**3,25** ***	**1,67** ***	**7,92** ***
		±SEM	0.17	0.13	0.14	0.19
	IR/XG-102	**mean**	**2,25** ++	**2,67** +	**2.00**	**6,92** +
		±SEM	0.13	0.14	0.12	0.26
Protocol 3	Sham/vehicle	**mean**	**0.00**	**0.00**	**0.10**	**0.10**
		±SEM	0.00	0.00	0.10	0.10
	IR/vehicle	**mean**	**3,33** ***	**2,44** ***	**2,00** ***	**7,78** ***
		±SEM	0.17	0.24	0.17	0.28
	IR/XG-102	**mean**	**2,27** ++	**2.36**	**2.27**	**6.91**
		±SEM	0.20	0.03	0.20	0.37

Values represent mean ± SEM(n=9-12/group)
***P<0.001 *vs* Sham/vehicle
+P<0.05; ++ P<0.01 *vs* IR/vehicle (Mann Whitney test)

A Representative images of HE stained kidney sections
B Quantification of tubular damages by score system

+ In male SD rats, bilateral kidney IR induced a significant increase of tubular degeneration and necrosis, tubular cast and basophilic tubules
+ XG-102 reduced the severity of tubular damages. In XG-102 treated rats, the number of tubules affected was lower and the lesions were mostly limited to the cortico-medullary junction and not extended to the superficial cortex compared to vehicle treated animals.

Bilateral renal IR in rats induced impaired kidney function and severe tubular damages. XG-102 administered i.v. before or after IR reversed kidney tubular lesions induced by IR injury. However, XG-102 seems to be more efficient when administered preventively (1 hour before IR; Protocol 2) showing a beneficial effect on both kidney function and tubular damages. These results suggest that JNK inhibition before IR injury can represent a pharmacological strategy to prevent acute kidney injury occurring in humans.

References

1) Kanellis J et al, Nephrol Dial Transplant, 25:2898-908, 2010.

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