Effect of Tadalafil 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 uninephrectomised rodents are widely used to study the effect of therapeutic and preventing strategies during surgical procedures in humans. Unilateral nephrectomy exacerbates post-ischemic tubular damages, mimicking a severe form of acute kidney injury. Previous studies demonstrated that phosphodiesterase type 5 (PDE5) inhibitors, attenuates renal IR injury by decreasing leukocytes infiltration (1) or by reducing urinary injury markers (2).

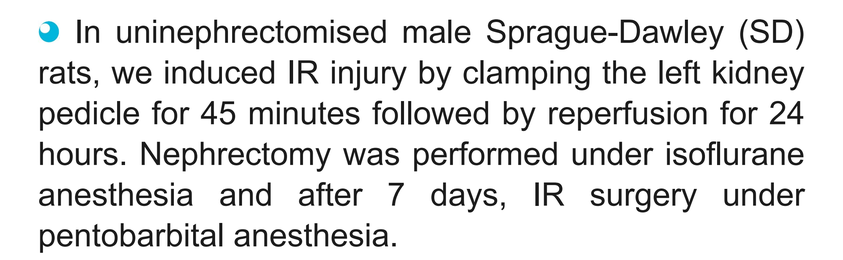
Aim

The aim of our study was to evaluate the preventive effect of Tadalafil, a selective PDE5 inhibitor, on kidney function and histological lesions after IR injury in uninephrectomised rats (NIR model: Nephrectomy + Ischemia + Reperfusion).

Methods

- In uninephrectomised male Sprague-Dawley (SD) rats, we induced IR injury by clamping the left kidney pedicle for 45 minutes followed by reperfusion for 24 hours. Nephrectomy was performed under isoflurane anesthesia and after 7 days, IR surgery under pentobarbital anesthesia.
- Renal function was determined by plasmatic and urinary creatinine and urea quantification.
- Kidney histological lesions were evaluated by hematoxylin eosin staining and histopathological analysis.
- Tadalafil or its vehicle (0.5 % methylcellulose and 0.05 % Tween 80 in distilled water) were administrated by gavage (10 mg/kg p.o.) at 24 hours and 15 minutes prior to ischemia.
- Sham-operated animals underwent the same surgical procedure and vehicle treatment without clamping of renal pedicle.

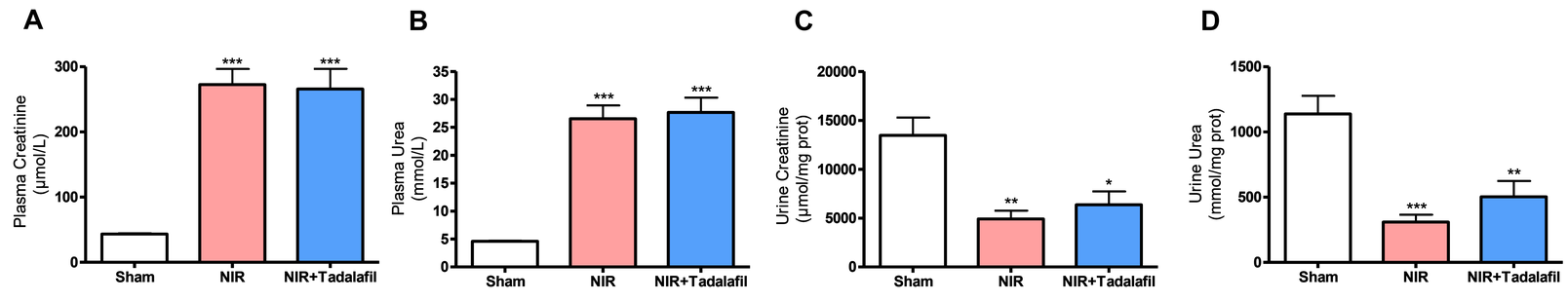
Experimental protocol



Group	Treatment	n
Sham	Nephrectomy + vehicle	8
NIR	Nephrectomy + IR + vehicle	10
NIR + Tadalafil	Nephrectomy + IR + tadalafil	10

Results

Effect of Tadalafil on kidney function biomarkers

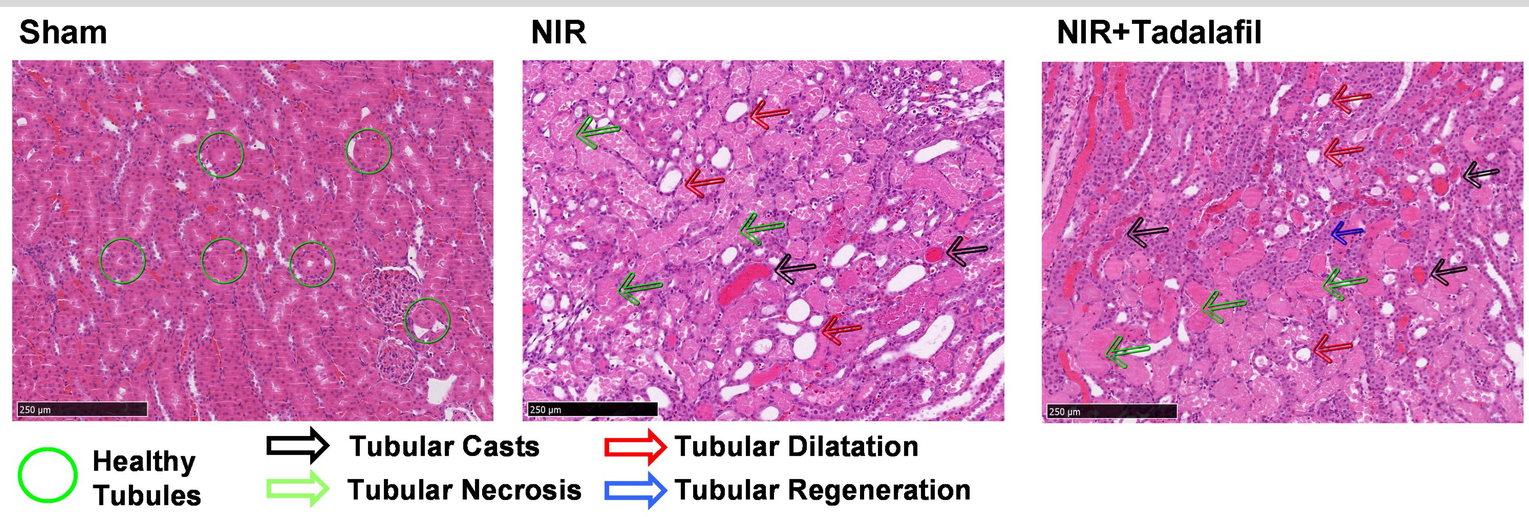


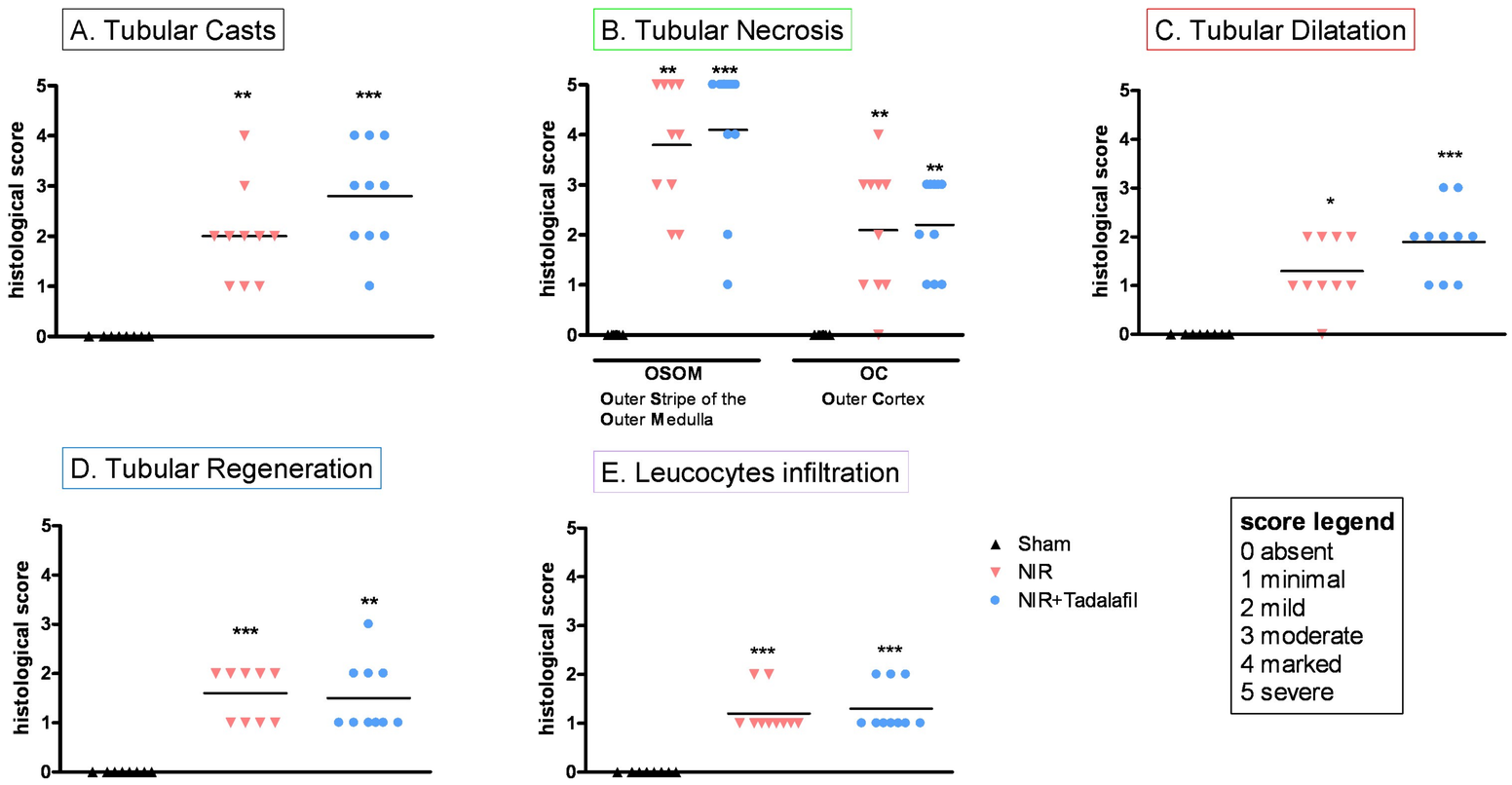
***P<0.001 ; **P<0.01; * P<0.05 vs Sham (one-way ANOVA followed by a Bonferroni test)

In male SD rats, renal ischemia-reperfusion in nephrectomised animals induced:
- a significant increase of plasmatic creatinine (Fig. A) and urea (Fig. B);
- a significant decrease of urinary creatinine (Fig. C) and urea (Fig. D).

Our result show that Tadalafil has no protective effects on impaired kidney function induced by ischemia-reperfusion injury.

Effect of Tadalafil on post-ischemic kidney lesions





* P<0.05;**P<0.01; ***P<0.001 vs Sham (Kruskal-Wallis followed by Dunn's test)

- Histological analysis revealed adequate and successful lesion induction in NIR animals compared to Sham, including tubular casts (A) and necrosis (B), tubular dilatation (C) and regeneration (D), inflammation and leucocytes infiltration (E).

Our result showed that Tadalafil had no effects on post-ischemic kidney lesions.

Conclusions

Previous studies (1,2,3) demonstrated that the selective PDE5 inhibitors, Sildenafil and Tadalafil, attenuate acute kidney injury following IR. However, these data were obtained in the early phase of reperfusion (60-240 minutes). Our study shows that Tadalafil administered 24h and 15 minutes prior to ischemia has no beneficial effect at 24 hours of reperfusion. Our results suggest the important role of timing of administration and therapeutic window for drug treatments. However, since our experimental conditions were not fully comparable to the protocols used by others, further studies are necessary to understand the potential of PDE5 inhibitors in ischemic tolerance and to prevent kidney damage during transplantation.

References

1) Oruc O et al, Acta Histochemica, 112:377-344, 2010.
2) Sohotnik R et al, Am J Physiol Renal Physiol, 304:F1099-104, 2013.
3) Gozeloglu M et al, Urol Int, 86:197-203, 2011

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