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Suramin promotes recovery from renal ischemia/reperfusion injury in mice

Shougang Zhuang[1], Bo Lu[2], Rebecca A. Daubert[3], Kenneth D. Chavin[2], Liquan Wang[4] and Rick G. Schnellmann[3]

[1]Department of Medicine, Brown University School of Medicine, Providence, Rhode Island, USA; [2]Department of Surgery, Medical University of South Carolina, Charleston, South Carolina, USA; [3]Department of Pharmaceutical and Biomedical Sciences, South Carolina College of Pharmacy, Medical University of South Carolina, Charleston, South Carolina, USA and [4]Department of Pathology, Brown University School of Medicine, Providence, Rhode Island, USA

Suramin is a polysulfonated naphthylurea originally designed as a treatment for trypanosomiasis; but that has also been used to treat rodent models of fulminant hepatic failure and focal brain ischemia. In this study, we determined the effects of suramin on renal ischemia/reperfusion-induced acute kidney injury in mice, in particular its effect when administered after renal injury has been established. Increasing concentrations of suramin were given 24 hours following reperfusion, a time when serum creatinine levels were at their highest level. This treatment improved renal function, as evidenced by decreased blood urea nitrogen and serum creatinine to control values and diminished histopathologic tubular damage. Suramin-treated animals had a significant reduction in apoptotic tubular cells and infiltrating leukocytes. There was also an increase of proliferating tubular cells following reperfusion compared to the number found in untreated animals. Our study shows that suramin promotes the recovery of renal function and has effective therapeutic applications when given after the occurrence of renal injury.

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Correspondence: *Rick G. Schnellmann, Department of Pharmaceutical and Biomedical Sciences, South Carolina College of Pharmacy, Medical University of South Carolina, 280 Calhoun St., POB 250140, Charleston, South Carolina 29425, USA. E-mail: schnell@musc.edu*

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Acute kidney injury (AKI) is a critical clinical problem with mortality at approximately 50%.[1] Renal ischemia/reperfusion (I/R) is a common cause of AKI. Although several decades of research have greatly improved our understanding of the mechanisms underlying renal tubular cell injury and death, and AKI, effective therapeutic interventions are still unavailable.

The pathogenesis of AKI is complex and varies to some extent based on the particular cause. Numerous studies have demonstrated that renal tubular death and tubulointerstitial inflammation are two important determinants of tissue damage and renal failure.[2,3] The proximal straight tubule in the outer medulla of the kidney is particularly susceptible to I/R injury. Damage to this segment is characterized initially by the disruption of tight junctions.[4] With more sustained I/R, epithelial cells of the proximal tubule undergo necrotic or apoptotic cell death.[5] The acute inflammatory response initiated by I/R is characterized by the generation of proinflammatory chemokines and cytokines.[3] Subsequently, the postischemic tissue is invaded by many pro-inflammatory leukocytes (neutrophils, macrophages, lymphocytes). These leukocytes have been recognized as important contributors to tissue damage through the release of oxygen-derived radicals and production of cytokines.[6]

Epithelial cells that do not die participate in the regeneration of tubular epithelium and the restoration of renal function. During the recovery process, renal epithelial cells dedifferentiate and then migrate and proliferate to replace lost cells.[7] Of those regenerative responses, proliferation is well studied in *in vitro* and *in vivo* systems. It has been shown that various growth factors such as epidermal growth factor, hepatocyte growth factor, and insulin-growth factor-1, enhance renal proximal tubular cells (RPTC) proliferation and accelerate the return of renal structure and function in experimental models of AKI.[1]

Unfortunately, similar beneficial effects of insulin-growth factor-1 were not observed in patients in clinical trials.[8,9] In one study, the patients did not develop acute renal failure,[8] whereas in the other study the patients very sick, had comorbid conditions, and there was a delay in insulin-growth

factor-1 administration.[9] Thus, whether agents that promote regeneration of tubular epithelium are effective in humans is unclear. Nevertheless, effective agents that can protect against renal injury and/or promote renal regeneration are needed.

Recently, it was reported that pre- or coadministration of suramin, a polysulfonated naphthylurea, protects the liver from injury caused by D-galactosamine and lipopolysaccharide in mice[10] and reduces brain damage induced by ischemia in rats.[11] The mechanism by which suramin protects these organs from injury remains incompletely understood, but may be associated with inhibition of apoptosis, and suppression of inflammatory cytokine production. Suramin preincubation inhibited tumor-necrosis factor-α and interleukin-6 production, tumor-necrosis factor-α and interleukin-6 mRNA expression, and nuclear factor-κB activity in macrophages[12] and release of interleukin-6 and monocyte chemoattractant protein-1 in human dermal endothelial cells.[13] In addition to these effects, we have shown that suramin can promote renal proximal tubular cell proliferation and scattering *in vitro*.[14] However, it is unknown whether suramin is beneficial in AKI.

In this study, we examined the effect of suramin on renal pathological changes and function in a murine model of renal I/R-induced AKI. Because drug treatment to prevent AKI is not usually possible, we examined the more relevant question of whether suramin promoted the return of renal function by administering suramin 24 h after I/R when serum creatinine levels were maximal. Renal tissue damage was assessed by measuring plasma blood urea nitrogen (BUN) and serum creatinine and by changes in renal histology. We also sought to determine the mechanism underlying suramin effects by examining the effect of suramin on apoptosis, leukocyte infiltration, and tubular cell proliferation.

RESULTS

Suramin treatment decreases BUN and creatinine levels

Numerous agents protect against AKI when administered before or at the time of reperfusion.[15] A treatment would be more clinically useful if it were effective when administrated after ischemia. To determine whether delayed administration of suramin promotes recovery of renal function in a murine model of AKI, mice were administered a variety of doses of suramin 24 h after release of the vascular clamps and reestablishment of blood flow. As shown in Figure 1, mice subjected to 26 min of renal I/R had significantly increased serum creatinine and BUN levels at 24 h and remained at these levels at 48 h after ischemic injury. Administration of suramin at 24 h after I/R injury reduced both BUN and creatinine levels compared with vehicle alone at 48 h after ischemia (Figure 1). The improvement of renal functions by suramin occurred in a dose-dependent manner with the maximum and complete effect observed at 0.1–1 mg/kg. Suramin at 10 mg/kg did not exhibit toxicity. These data reveal that suramin promotes recovery from I/R-induced AKI.

Suramin treatment decreases histopathologic damage to tubules

To determine if the surmain-induced functional changes were associated with histological changes, histological changes were examined 48 h after ischemia. Tubular dilatation, swelling, necrosis, luminal congestion, and hemorrhage were present in the kidneys of mice subjected to IR, but these changes were decreased in animals treated with suramin (Figure 2). Scoring of kidney sections for histopathologic damage to the tubules showed that suramin at 1 mg/kg decreased damage (Figure 2). Sham-operated mice incurred no tubular injury. Thus, suramin treatment decreased renal histological damage after I/R.

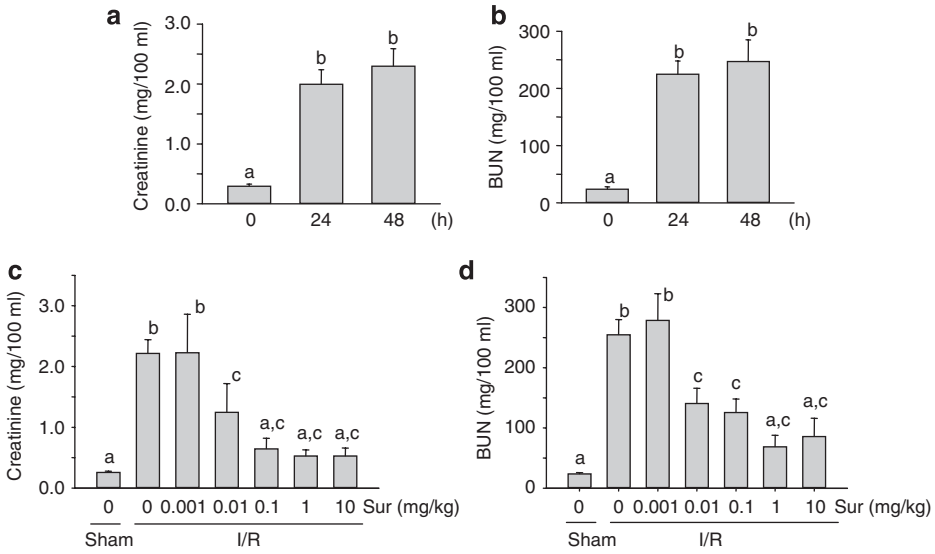

Figure 1 | Effect of delayed administration of suramin on creatinine and BUN in mice subjected to I/R. (**a**, **b**) Mice were subjected to 26 min of bilateral renal ischemia and then allowed to recover for 24 or 48 h. (**c**, **d**) Five groups of mice were subjected to suramin (Sur) treatment at 24 h after release of renal clamps at the indicated doses. Serum creatinine and BUN levels were measured. Data are shown as means ± s.d. Bars with different letters are significantly different from each other ($P < 0.05$).