MITOCHONDRIA-TARGETED ANTIOXIDANT SKQR1 PREVENTS ENDOTHELIAL DYSFUNCTION DURING ISCHEMIC ACUTE KIDNEY INJURY

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INTRODUCTION AND AIMS:
Ischemia and reperfusion (I/R) of kidney is one of the leading causes of the acute kidney injury (AKI). I/R leads to mitochondrial dysfunction and overproduction of reactive oxygen species. Oxidative stress could affect endothelial function and this may be explanation for deterioration of renal hemodynamics observed during AKI. The aim of this work to study the ability of mitochondria-targeted antioxidant SkQR1 to prevent endothelial dysfunction of kidney during I/R.

METHODS:
EaHy926 cells were exposed to 5 hrs of oxygen-glucose deprivation (OGD) to study the effect of I/R on endothelium in vitro. Cell viability was measured by MTT 24 hrs after OGD.
I/R of left kidney was performed in male rats to study ischemic AKI in vivo. Renal pedicle of left kidney was clamped for 40 min and the right kidney was removed. The severity of renal failure was assessed by the serum levels of creatinine (SCr) and blood urea nitrogen (BUN) 48 hrs after I/R. Renal blood flow (RBF) was measured by high frequency ultrasound Doppler system. MRI was used to visualise renal vasculature. Accumulation of Evans Blue dye in kidney parenchyma 70 min after intravenous injection was used to assess permeability of renal vasculature 48 hrs after I/R.

RESULTS:
OGD decreased viability of cells to 48%. I/R in vivo resulted in pronounced increase of SCr and BUN (4.2 and 5.7 times respectively vs control rats). 10 min after I/R we observed the collapse of intrarenal arteries. 30 min after IR RBF was 48% of preischemic values and renal artery resistance index (RI) was increased from 0.67 (preischemia) to 0.89. 48 hrs after I/R the amount of Evans Blue dye penetrated into kidney parenchyma increased from 0.82 to 1.06 ng/mg kidney weight (vs control rats) indicating augmentation of renal vascular permeability.
Preincubation with SkQR1 (25nM) for 1 hrs increased viability of OGD-exposed EaHy926 cells to 64%. Treatment of rats with SkQR1 (100 nmol/kg i.p.) 3 hrs before and 1, 18, 30 and 42 hrs after I/R diminished SCr and BUN levels to 56% and 53% respectively (vs I/R rats) and attenuated endothelial dysfunction. 30 min after I/R RBF in SkQR1-treated rats increased to 67% of preischemic values and RI decreased to 0.64. The MRI scans revealed the lesser amount of collapsed vessels. Evans Blue penetration into kidney parenchyma decreased to 0.82 ng/mg kidney weight. Co-treatment of animals with SkQR1 and Nω-Nitro-L-arginine (1 mg/kg i.v. 15 min before I/R) abolished beneficial effect of SkQR1 both on renal function and renal hemodynamics.

CONCLUSIONS:
Mitochondria-targeted antioxidant SkQR1 attenuates endothelial dysfunction and renal failure after ischemic AKI.

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REFERENCES:

Protective effect of mitochondria-targeted antioxidants in an acute bacterial infection.

Plotnikov E.Y., Morosanova M.A., Pevzner I.B. et al., PNAS 2013

Mitochondria-targeted antioxidant SkQR1 ameliorates gentamycin-induced renal failure and hearing loss.

Jankauskas S.S., Plotnikov E.Y., Morosanova M.A. et al., Biochemistry (Mosc). 2012

Mechanisms of nephroprotective effect of mitochondria-targeted antioxidants under rhabdomyolysis and ischemia/reperfusion.

Plotnikov E.Y., Chupyrkina A.A., Jankauskas S.S. et al., Biochim Biophys Acta. 2011

The role of mitochondria in oxidative and nitrosative stress during ischemia/reperfusion in the rat kidney.

Plotnikov E.Y., Kazachenko A.V., Vyssokikh M.Y. et al. Kidney Int. 2007

Nephroprotective effect of GSK-3β inhibition by lithium ions and δ-opioid receptor agonist dalargin on gentamicin-induced nephrotoxicity.

Plotnikov E.Y., Grebenchikov O.A., Babenko V.A. et al., Toxicol Lett. 2013

Mild uncoupling of respiration and phosphorylation as a mechanism providing nephro- and neuroprotective effects of penetrating cations of the SkQ family.

Plotnikov E.Y., Silachev D.N., Jankauskas S.S. et al., Biochemistry (Mosc). 2012

The phenoptosis problem: what is causing the death of an organism? Lessons from acute kidney injury.

Zorov D.B., Plotnikov E.Y., Jankauskas S.S. et al., Biochemistry (Mosc). 2012

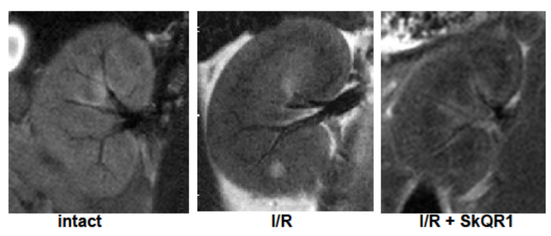
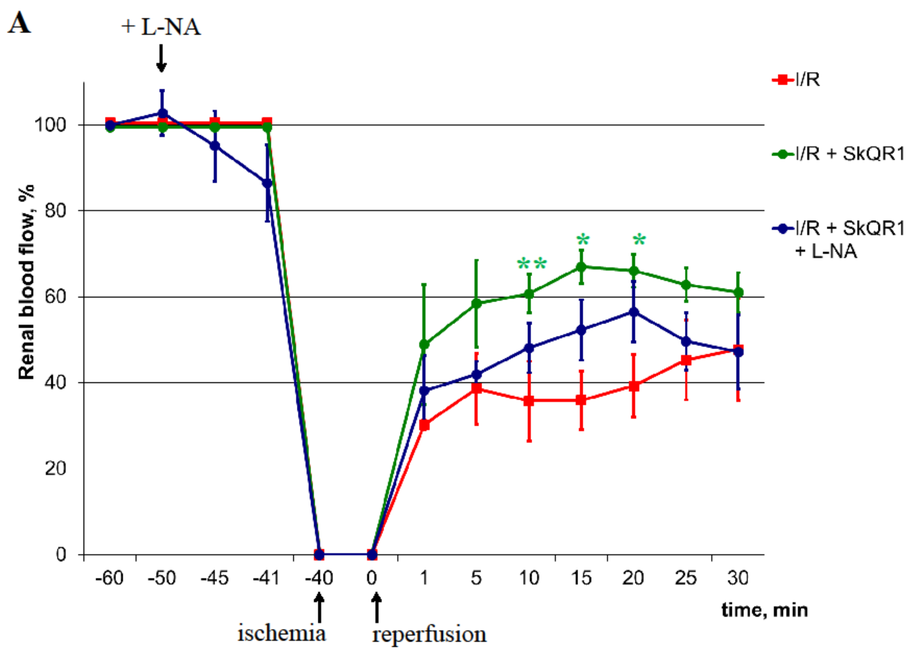
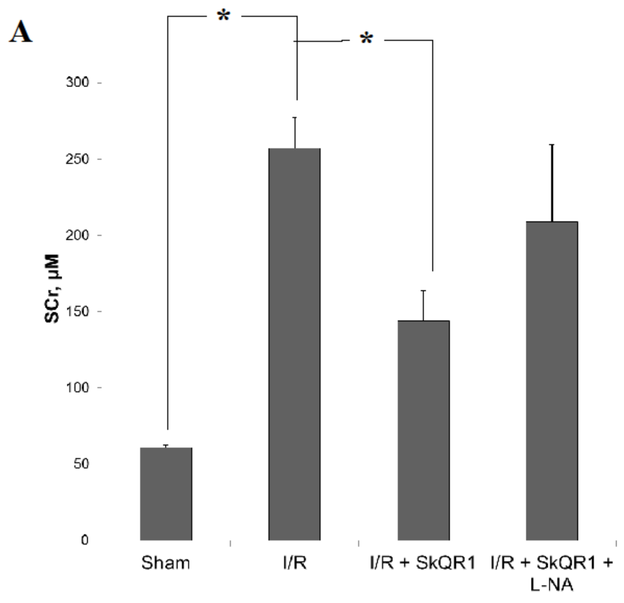
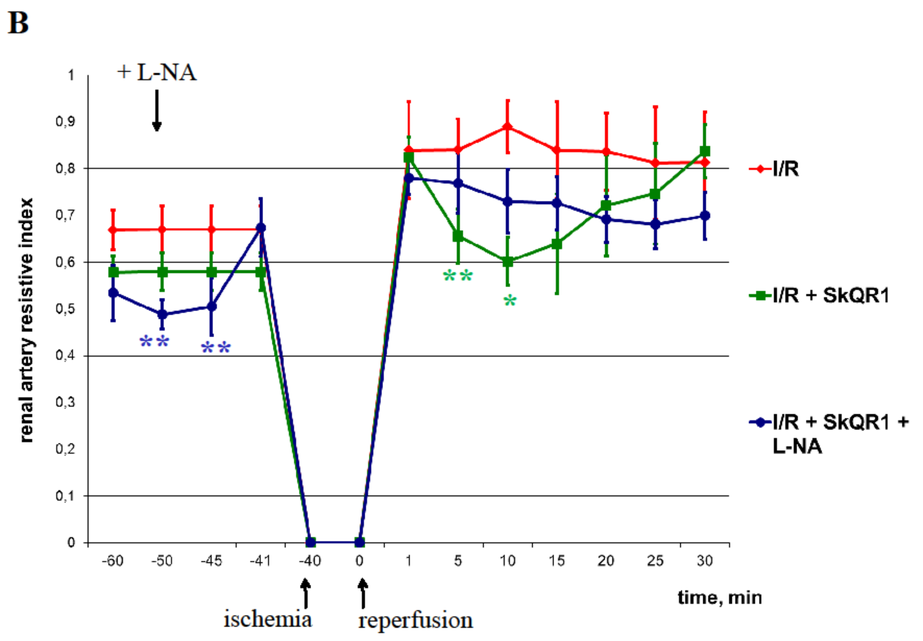


Fig. 2. SkQR1 mitigates I/R- induced collapse of intrarenal arteries.

MRI scans of kidney after 40 min of ischemia and 10 of reperfusion of kidney. SkQR1 (100 nmol/kg i.p.) was administered 3hrs before I/R.







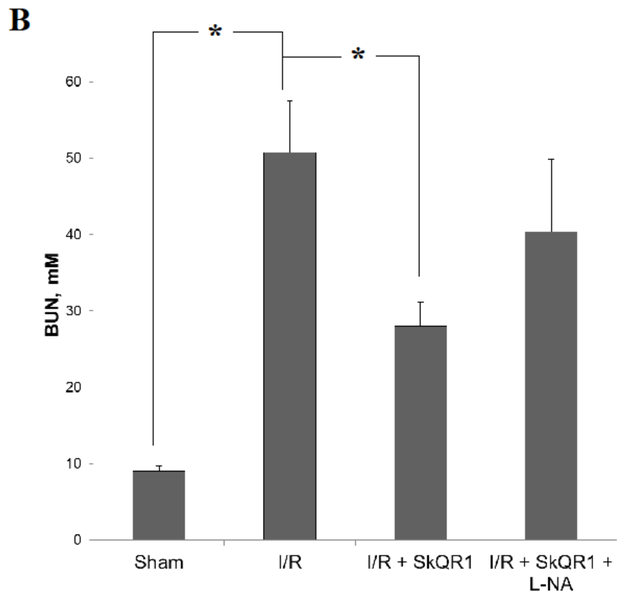


Fig. 3. SkQR1 mitigates I/R-induced renal failure. Nω-nitro-L-arginine abolishes this effect.
A -Serum creatinine (SCr) 48 hrs after I/R.
B - blood urea nitrogen (BUN) 48 hrs after I/R.
SkQR1 (100 nmol/kg i.p.) was administered 3 hrs before and 1, 18, 30, 42 hrs after I/R. 1mg/kg Nω-nitro-L-arginine (L-NA) was administered i.v. 10 min before I/R.
* - p<0,001

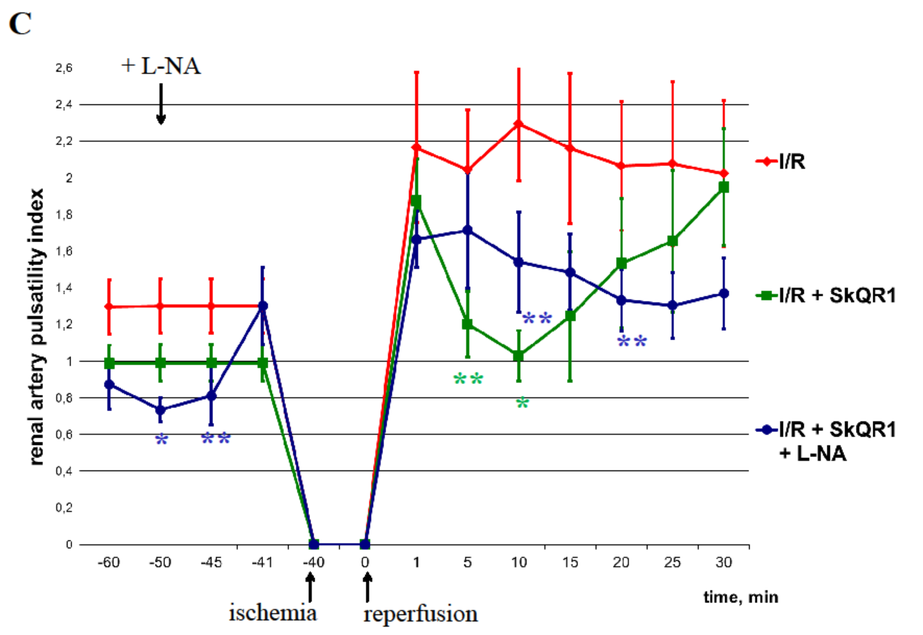


Fig. 4. SkQR1 mitigates I/R-induced abnormalities of renal hemodynamics. Nω-nitro-L-arginine abolishes this effect.

High frequency Doppler transducer was used to measure blood flow velocity in renal artery. Renal blood flow, resistive index and pulsatility index were calculated. 1 mg/kg Nω-nitro-L-arginine (L-NA) was administered i.v. 10 min before I/R . 100 nmol/kg SkQR1 was administered i.p. 3 hrs before I/R.
* - p<0,05 ** - p<0,1 vs «I/R».

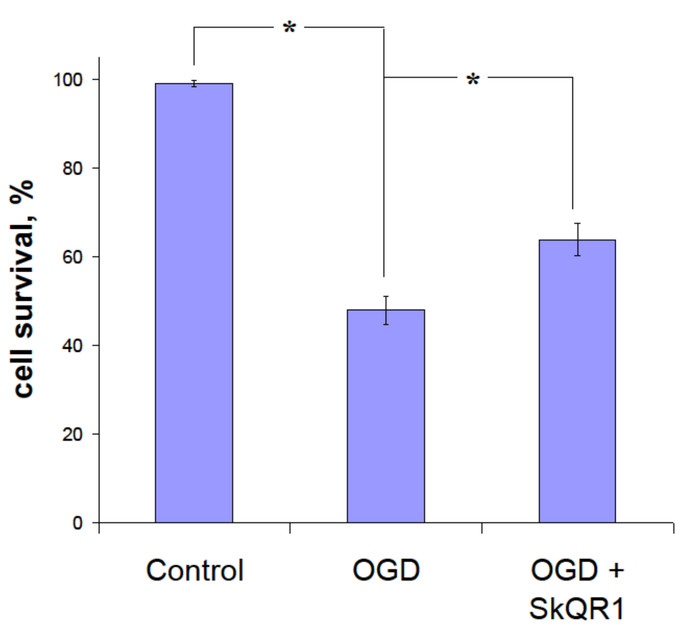
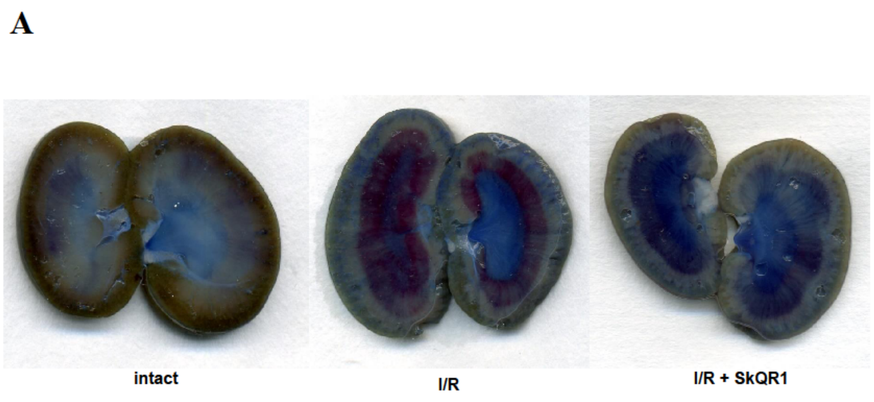


Fig. 1. SkQR1 diminishes endothelial cell death after oxygen-glucose deprivation (OGD).

EaHy926 cells were exposed to 5 hrs of OGD and 24 hrs after the amount of viable cells was determined by MTT assay. Cells were incubated with SkQR1 (25 нМ) for 1 hrs before OGD in "OGD + SkQR1" group.

* - p<0,05



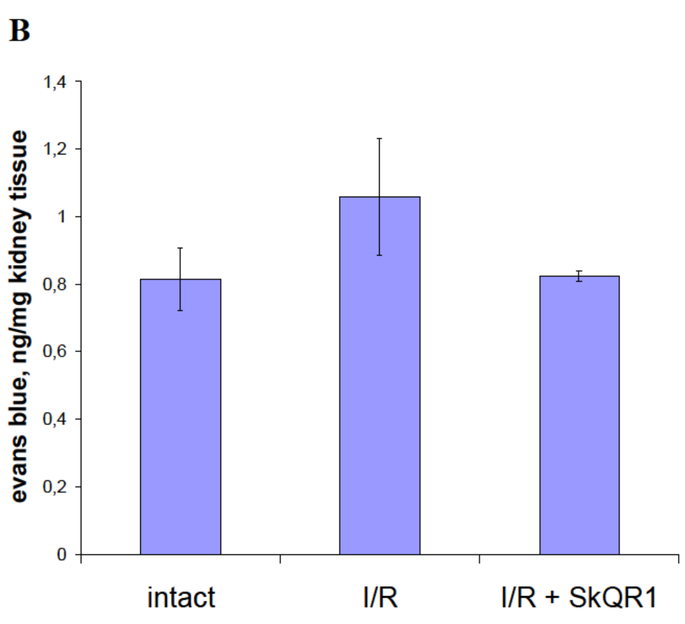


Fig. 5. SkQR1 prevents I/R-induced increase of vascular permeability in kidney.

A – kidneys of intact rat, rat 48 hrs after I/R and rat 48 hrs after I/R and SkQR1 treatment (100 nmol/kg i.p. 3 hrs before and 1, 18, 30, 42 hrs after I/R). 0,5% Evans Blue was injected i.v. and kidneys were excised 70 after injection.

B – the amount of Evans Blue extracted from kidneys of intact rats rat 48 hrs after I/R and rat 48 hrs after I/R and SkQR1 treatment.

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