SIGMA-1 RECEPTOR AGONISM IS PROTECTIVE AGAINST RENAL ISCHEMIA/REPERFUSION INJURY

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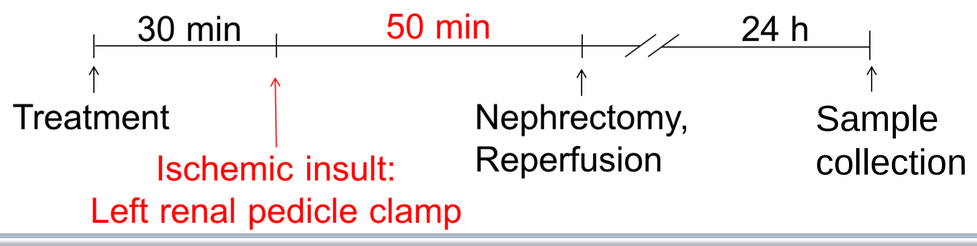
Introduction and Aims

- Renal ischemia/reperfusion (I/R) injury-induced acute kidney injury is associated with high mortality and effective therapies are lacking [1]
- Activation of **Sigma-1 receptor (S1R)** is protective against hypoxic injury of the heart and brain [2, 3]
- **SA-4503 (SA) i**s a potent, selective S1R agonist [4]
- Here in a **rat model of renal I/R** we investigated the effect of SA-4503 on renal structural and functional damage and on the **S1R – nitric oxide sythase (NOS) signaling pathway**

Methods

- ***In vivo* model:**
  male Wistar rats
  190±10g
  n=8-12/ group
  - **SHAM**: sham operated healthy controls
  - **I/R**: isotonic saline
  - **I/R SA** : specific S1R agonist SA-4503 (1 mg/bwkg)
  - **I/R SAN**: SA-4503 + S1R antagonist NE100 (1 mg/bwkg)

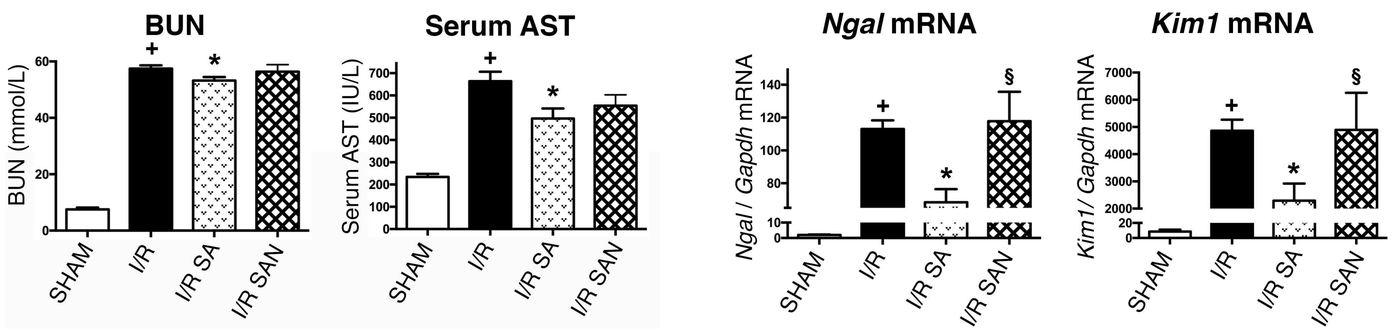


- ***In vitro* model:**
  HK-2 human proximal tubular cells
  - **Control (C)**
  - **SA** : S1R agonist SA-4503: 10µM
  - **FLU**: S1R agonist fluvoxamine (FLU): 10µM
  - **PRE:** S1R agonist PRE-087 (PRE): 10µM

- Histology: PAS-stained kidney sections
- *Ngal, Kim1*: RT-qPCR
- S1R, pAkt, peNOS protein: Western blot
- NO concentration: Griess method

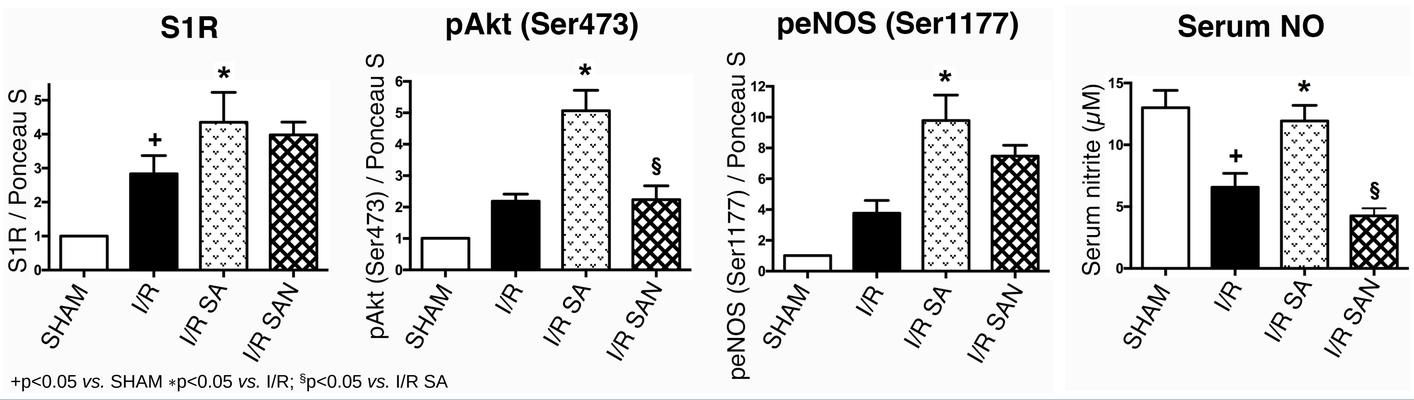
Results

Impaired kidney function and tubular damage following I/R were ameliorated by S1R agonist SA-4503



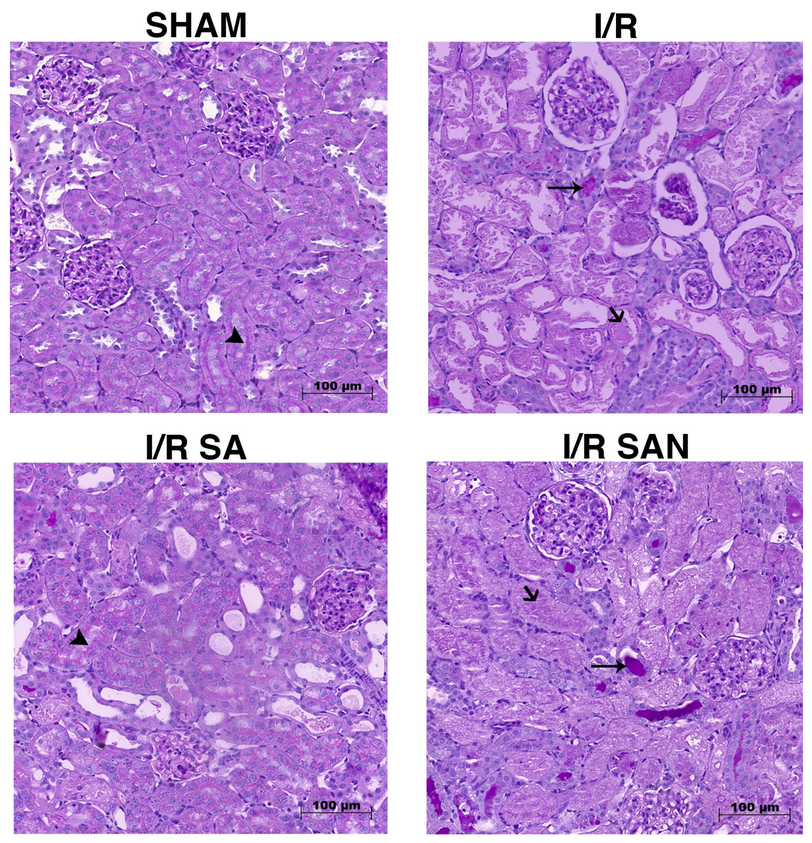
+p<0.05 *vs.* SHAM ∗p<0.05 *vs.* I/R; §p<0.05 vs. I/R SA

SA-4503 activated S1R – Akt – eNOS signaling and induced NO production



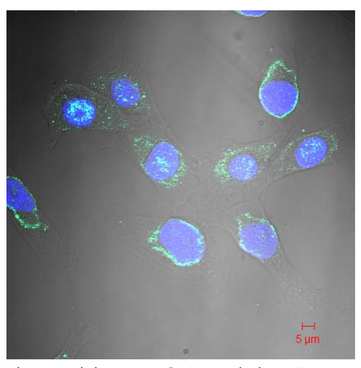
+p<0.05 *vs.* SHAM ∗p<0.05 *vs.* I/R; §p<0.05 *vs.* I/R SA

Renal structural damage was mitigated by SA-4503



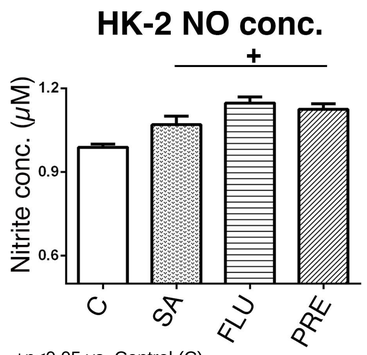
PAS-stained kidney sections. Black arrowheads point to intact brush borders, short arrows point to necrotic tubules, long arrows show hyalin accumulation, 200x magnification, scale bar=100µm

Localization of S1R in proximal tubular cells



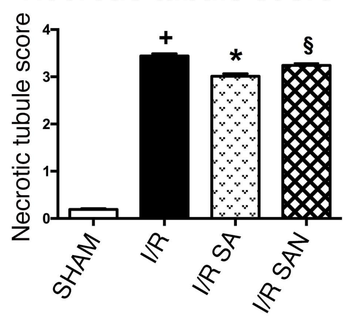
Blue: nuclei, green: S1R; scale bar=5 µm

S1R agonists induced NO production in proximal tubular cells



+p<0.05 vs. Control (C)

Necrotic tubule score



+p<0.05 vs. SHAM ∗p<0.05 vs. I/R; §p<0.05 vs. I/R SA

Conclusions

The specific and high affinity **S1R agonist SA-4503** acts directly on proximal tubular cells by activating the **S1R-NOS** system. Thereby SA-4503 is renoprotective by **increasing vasodilative NO production** and thus improving post-ischemic renal perfusion.
Based on our data S1R activation could provide a new option for renoprotective therapy.

References

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