THE ANTIDEPRESSANT FLUVOXAMINE IS PROTECTIVE AGAINST RENAL ISCHEMIA/REPERFUSION INJURY

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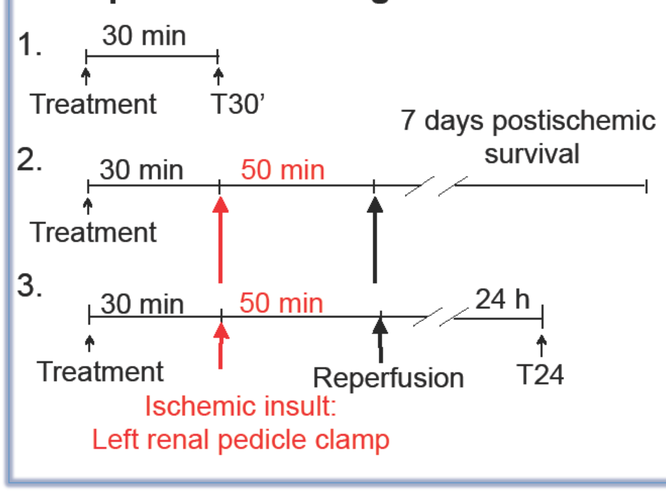
Introduction and Aims

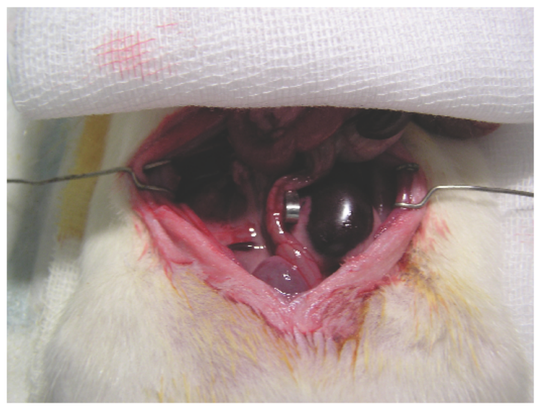
- Activation of **Sigma-1 receptor (S1R)** is protective against ischemia/reperfusion (I/R) injury in the heart and brain *(Bhuiyan, 2011)* via the induction of **Akt- endothelial nitric oxide synthase (eNOS)** pathway *(Tagashira, 2011)*.
- The antidepressant **fluvoxamine (FLU)** is a potent S1R agonist *(Maurice, 2001)*.
- **Here we investigate the effect of FLU in a rat and *in vitro* model of renal I/R on postischemic survival and on the S1R - NOS signal transduction pathway.**

Methods

- **Experimental design**



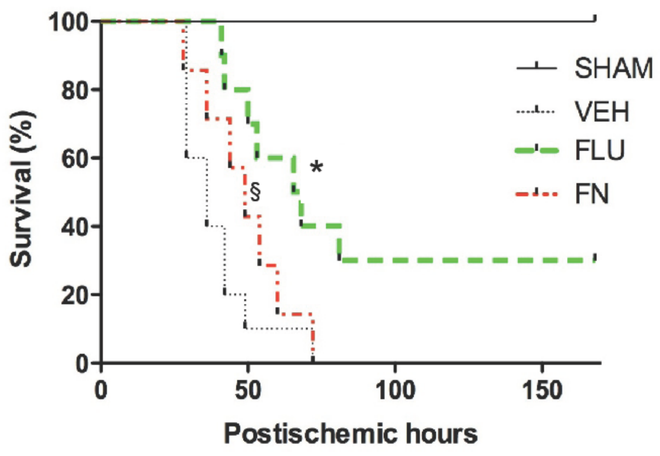
- **Treatment groups: male Wistar rats** (190±10g; n=8-12/ group)
  - **SHAM**: sham-operated healthy controls
  - **VEH**: isotonic saline + I/R
  - **FLU** : fluvoxamine (20mg/bwkg)
  - **FN**: FLU + specific S1R antagonist NE100 (1mg/bwkg)
  - **FLU + L-NAME**: FLU + non selective NOS blocker L-NAME (10mg/bwkg)
  - **FLU + L-NIO**: FLU + selective eNOS blocker L-NIO (20mg/bwkg)
  - **FLU + 7-NI**: FLU + selective nNOS blocker 7-NI (25mg/bwkg)



- Measurement of S1R, pAkt, PKA, peNOS and nNOS protein levels
- *In vivo* determination of intrarenal capillary hemodynamics by multiphoton microscopy (n=3/group, ~150 capillaries/animal)
- *In vitro* experiments: HK2 human proximal tubular cells treated with 400 µM H_2O_2 and 10 µM FLU (n=6/group)

Results

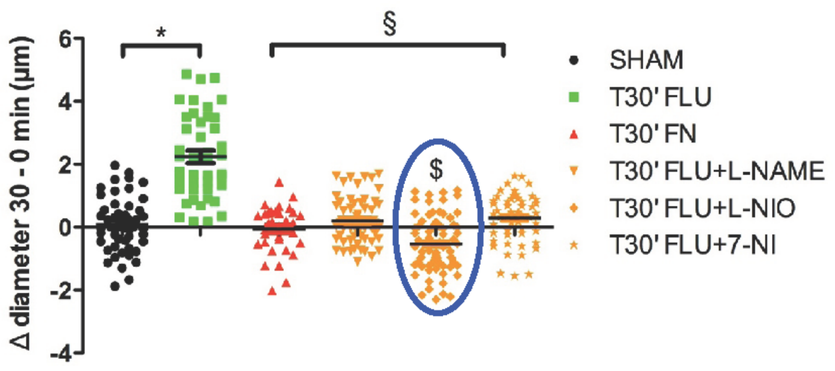
1. Primary end-point: FLU pretreatment prolongs postischemic survival



*p<0.05 vs. VEH, § p<0.05 vs.FLU, n=8/group

30 minutes (T30') - without I/R

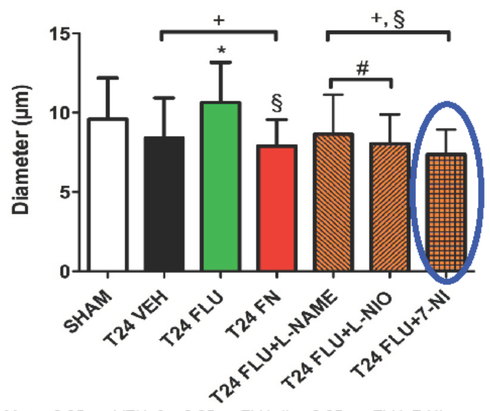
2. FLU induces ***intrarenal vasodilation*** without I/R. Since the eNOS blocker L-NIO shows the most effective inhibition of early vasodilation, this is likely to be mediated mainly by eNOS.



*p<0.05 vs. SHAM, §p<0.05 vs.FLU, $p<0.05 vs. FLU+7-NI

24 hours (T24) - after I/R

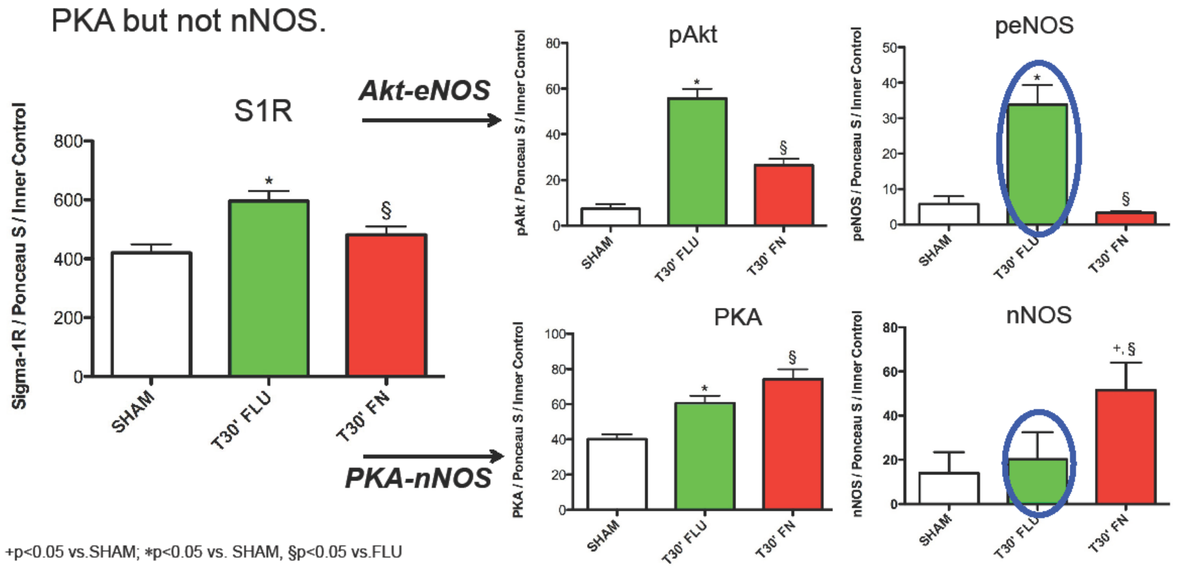
3. I/R induced ***vasoconstriction*** is prevented by FLU via S1R. Since the nNOS blocker 7-NI shows the most effective inhibition of long-term vasodilation, this is mediated mainly by nNOS.



+p<0.05 vs. SHAM, *p<0.05 vs. VEH, §p<0.05 vs.FLU, # p<0.05 vs. FLU+7-NI

30 minutes (T30') - without I/R

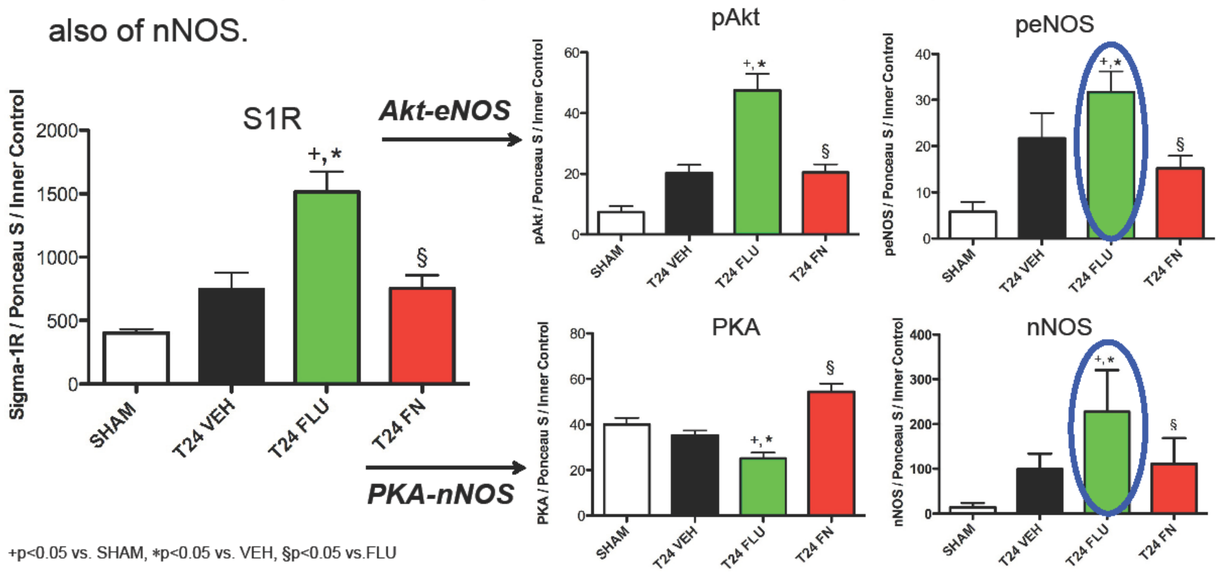
4. FLU induces a prompt increase in ***protein levels*** of S1R, pAkt, peNOS and PKA but not nNOS.



+p<0.05 vs.SHAM; *p<0.05 vs. SHAM, §p<0.05 vs.FLU

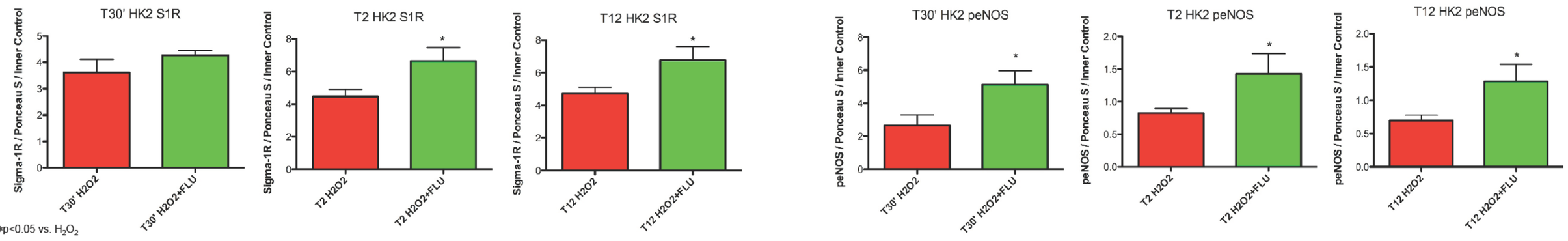
24 hours (T24) - after I/R

5. FLU increases postischemic ***protein levels*** of S1R, pAkt, peNOS and also of nNOS.



+p<0.05 vs. SHAM, *p<0.05 vs. VEH, §p<0.05 vs.FLU

6. FLU increases the ***protein levels*** of S1R and peNOS in human proximal tubular cells under oxidative stress.



*p<0.05 vs. H_2O_2

Summary

The antidepressant FLU improves postischemic survival and is protective against I/R induced renal damage. This protective effect is partly attributed to the S1R-NOS mediated intrarenal vasodilation induced by FLU in a NOS isoform and time specific manner.

This renoprotective effect of FLU could be used as a new therapeutic approach in pre- and post-transplantation therapy.

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