The Sigma-1 receptor: A novel drug target in renal disease

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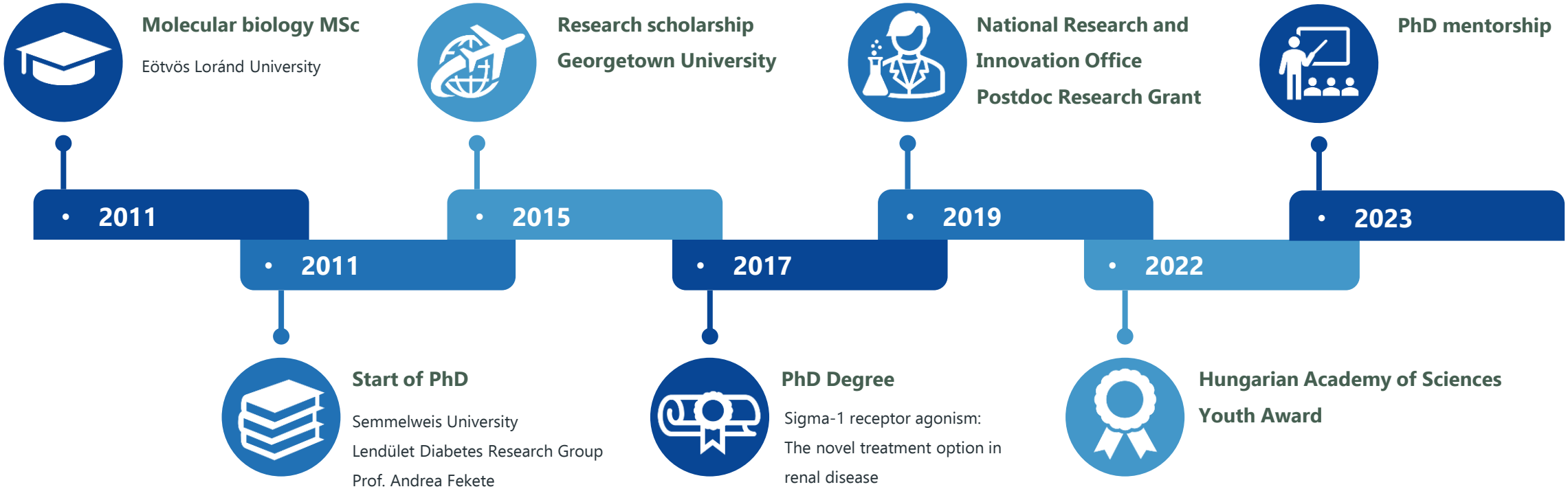
ABOUT ME

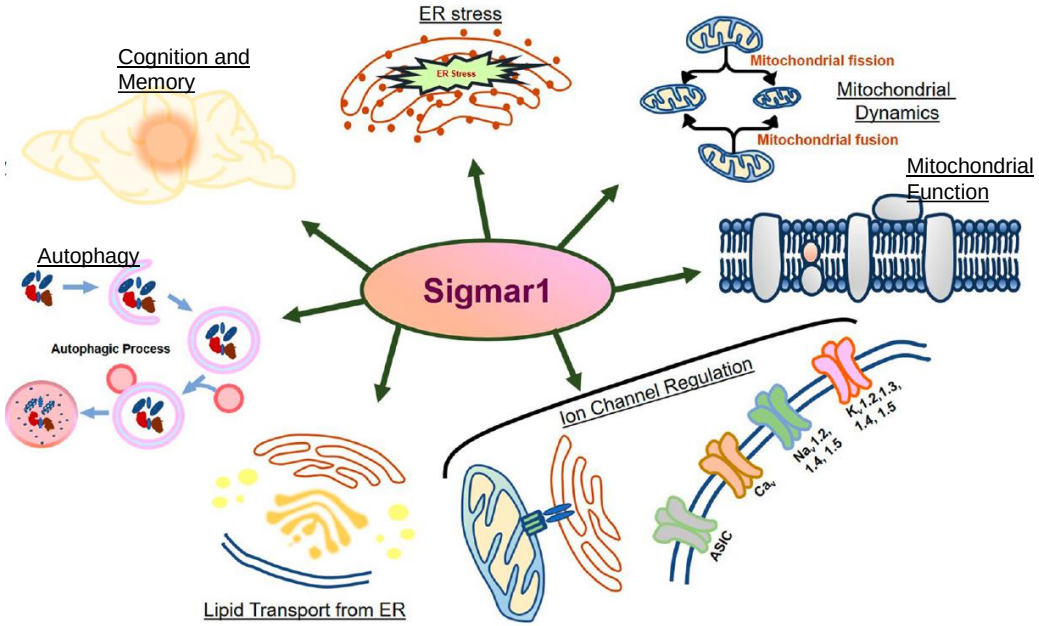

2011
Molecular biology MSc
Eötvös Loránd University
2011
Start of PhD
Semmelweis University
Lendület Diabetes Research Group
Prof. Andrea Fekete
2015
Research scholarship
Georgetown University
2017
PhD Degree
Sigma-1 receptor agonism:
The novel treatment option in
renal disease
2019
National Research and
Innovation Office
Postdoc Research Grant
2022
Hungarian Academy of Sciences
Youth Award
2023
PhD mentorship

THE **SIGMA-1 RECEPTOR** AND HOW IT ALL STARTED...

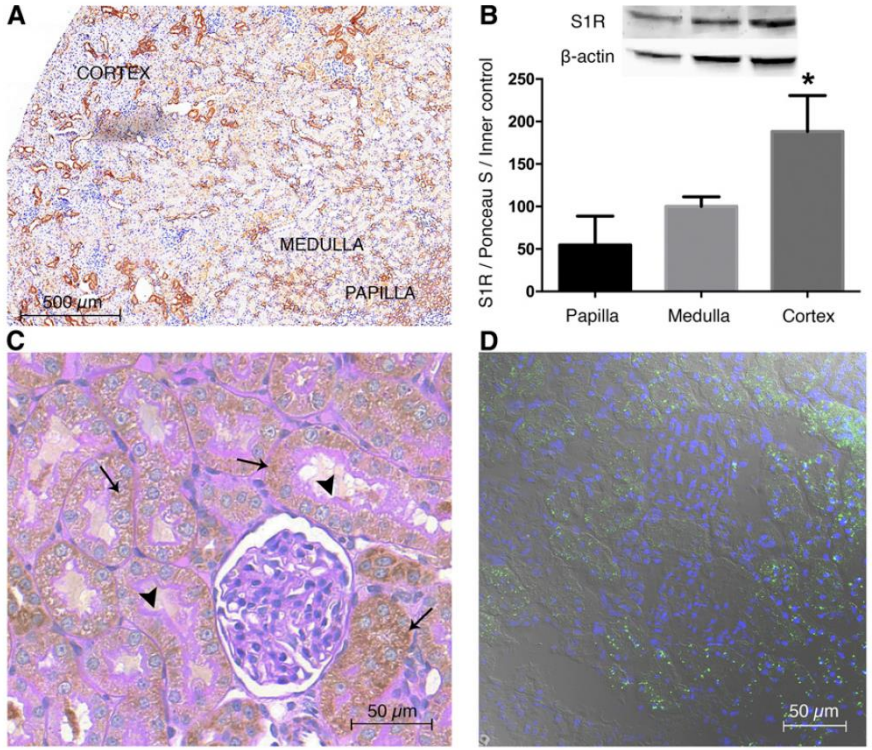
Chaperone protein in the central nervous system

Function:

- Memory, depression, substance abuse
- Ca^{2+} signaling, ion channel and mitochondrial function regulation, ER stress
- Protective in cerebral hypoxic injury



- Sigma-1 receptor (S1R) is expressed in the kidney
- Predominantly in proximal tubules

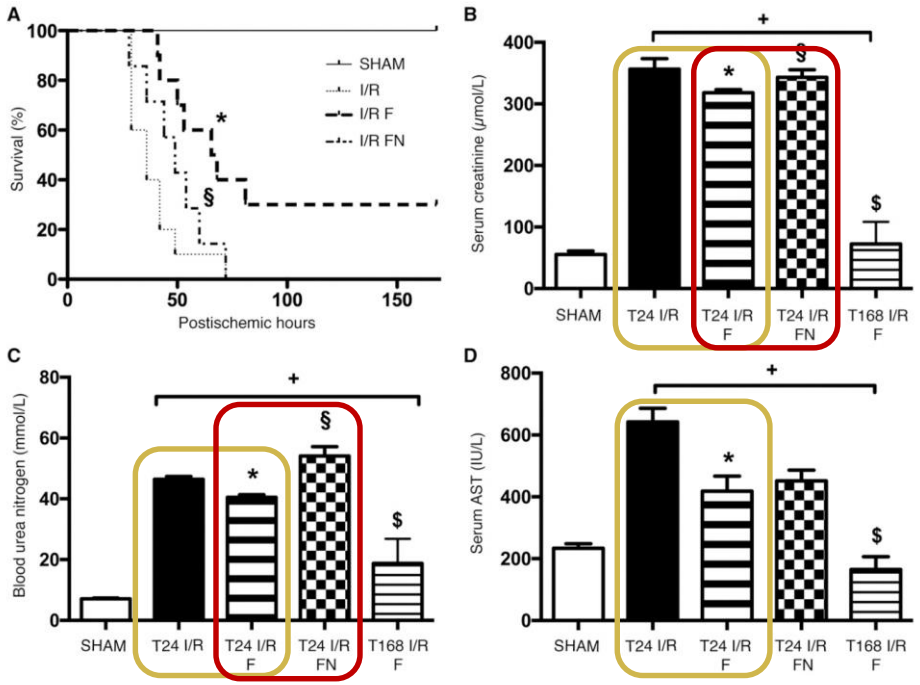


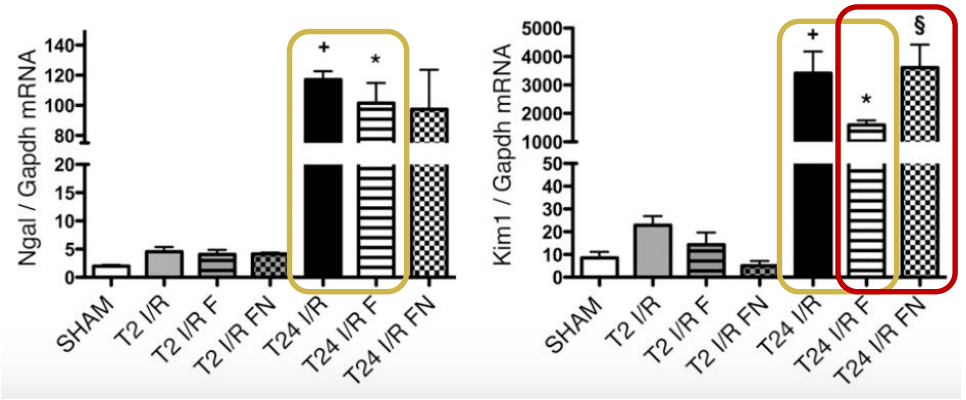
brown: S1R, blue: nuclei

green: S1R
blue: nuclei

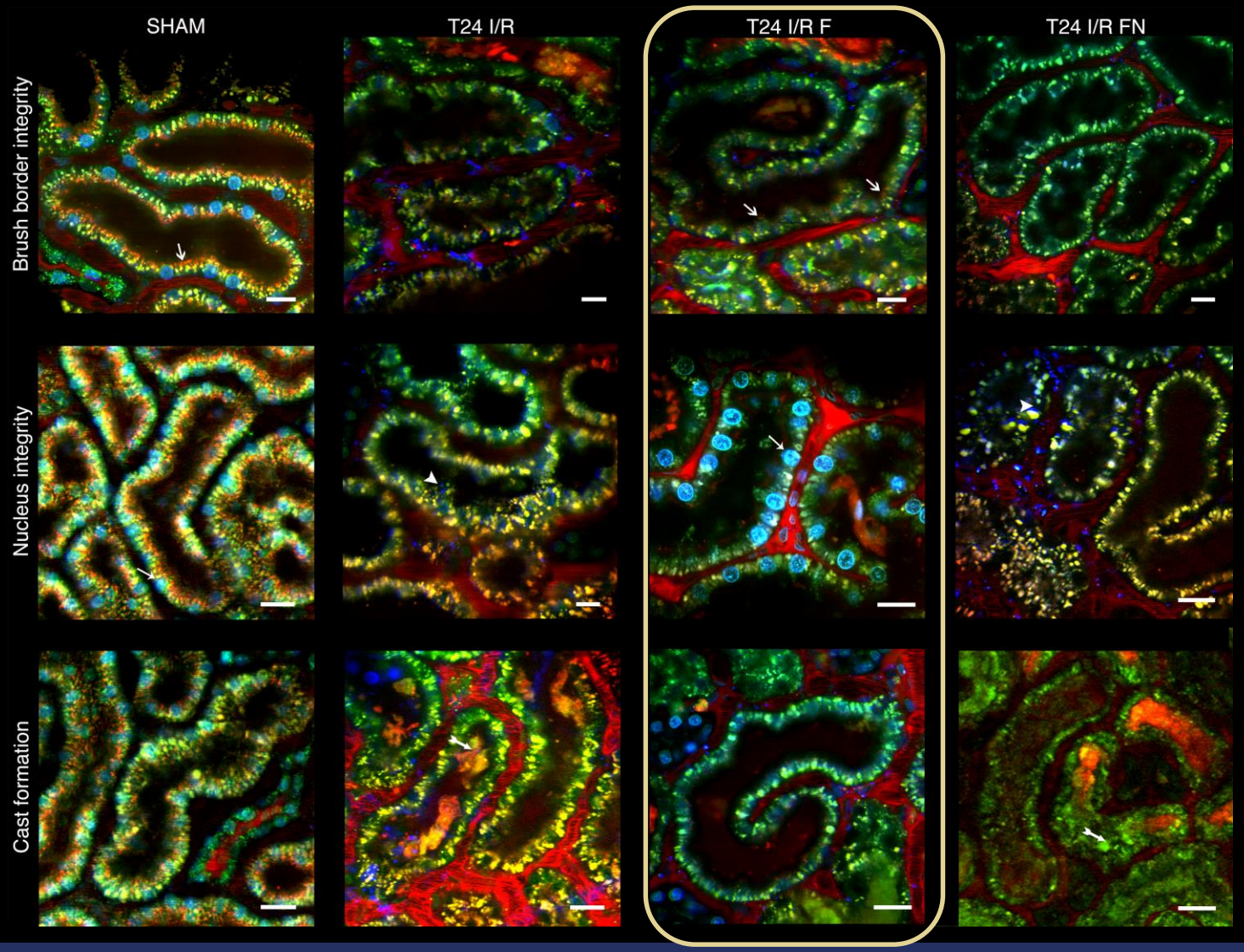
- A rat model of renal **ischemia/reperfusion injury**
- Rats treated with **S1R agonist Fluvoxamine (T24 IR F)**

- S1R agonist improves post-IRI survival and kidney function
- Attenuates tubular injury

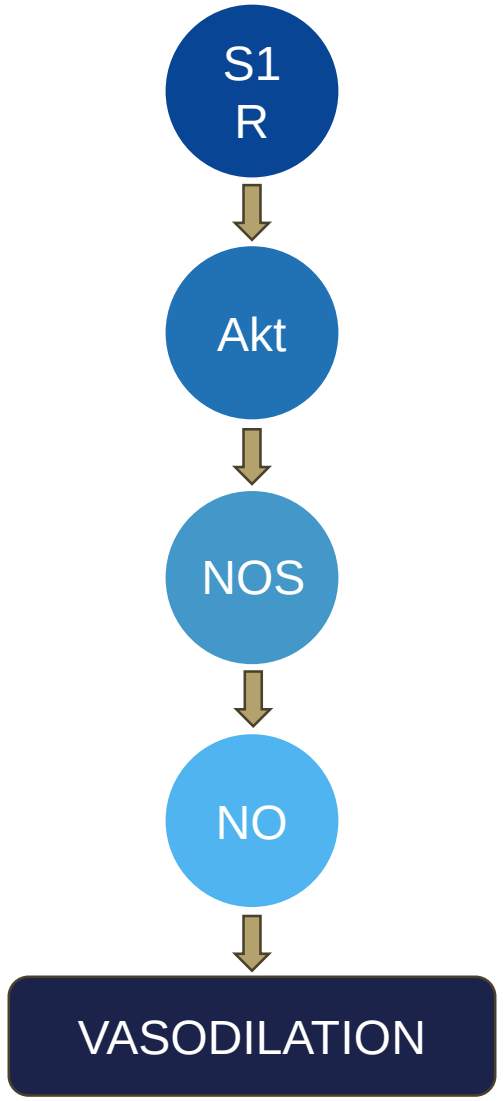


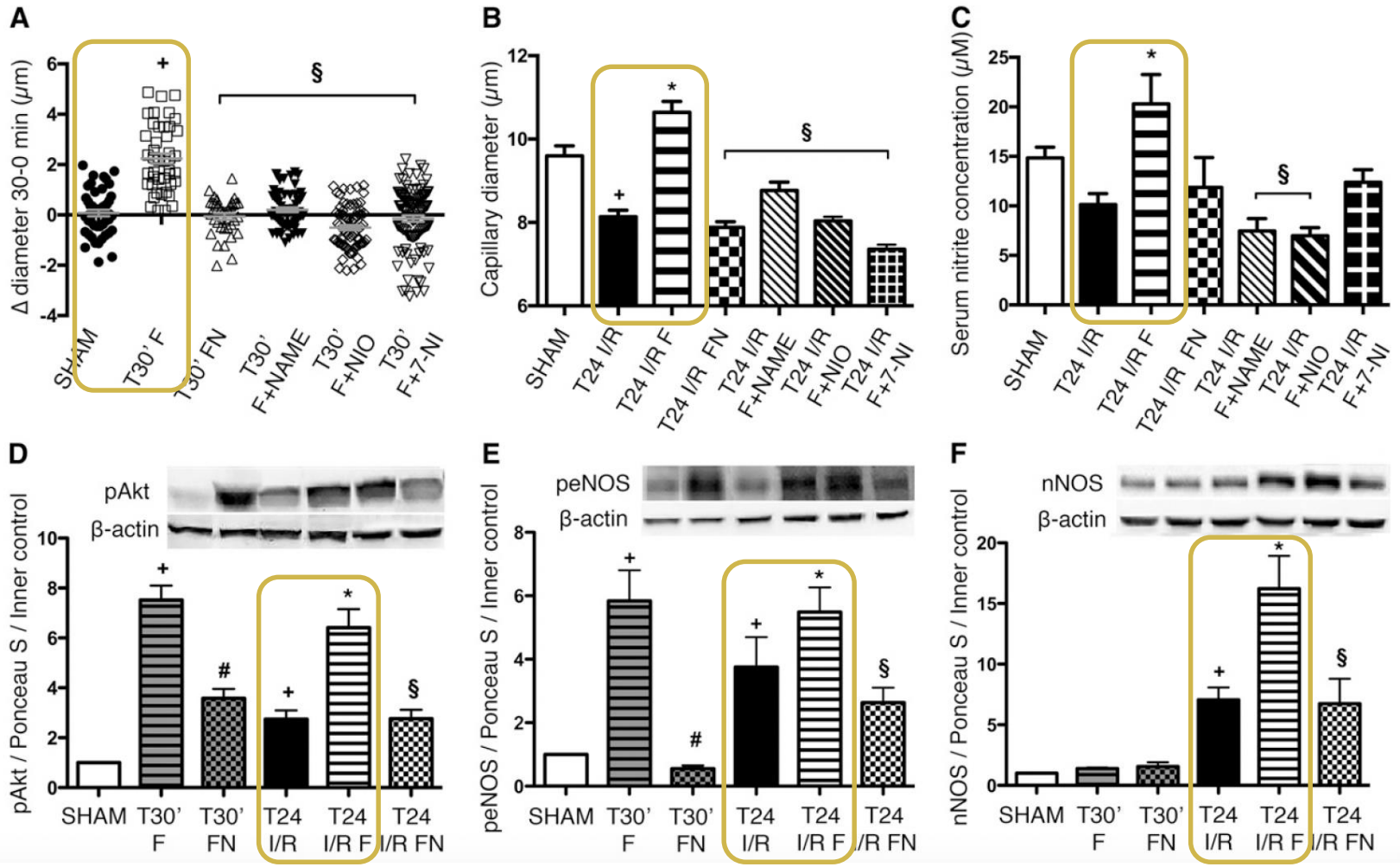


S1R agonist ameliorates renal cortical injury

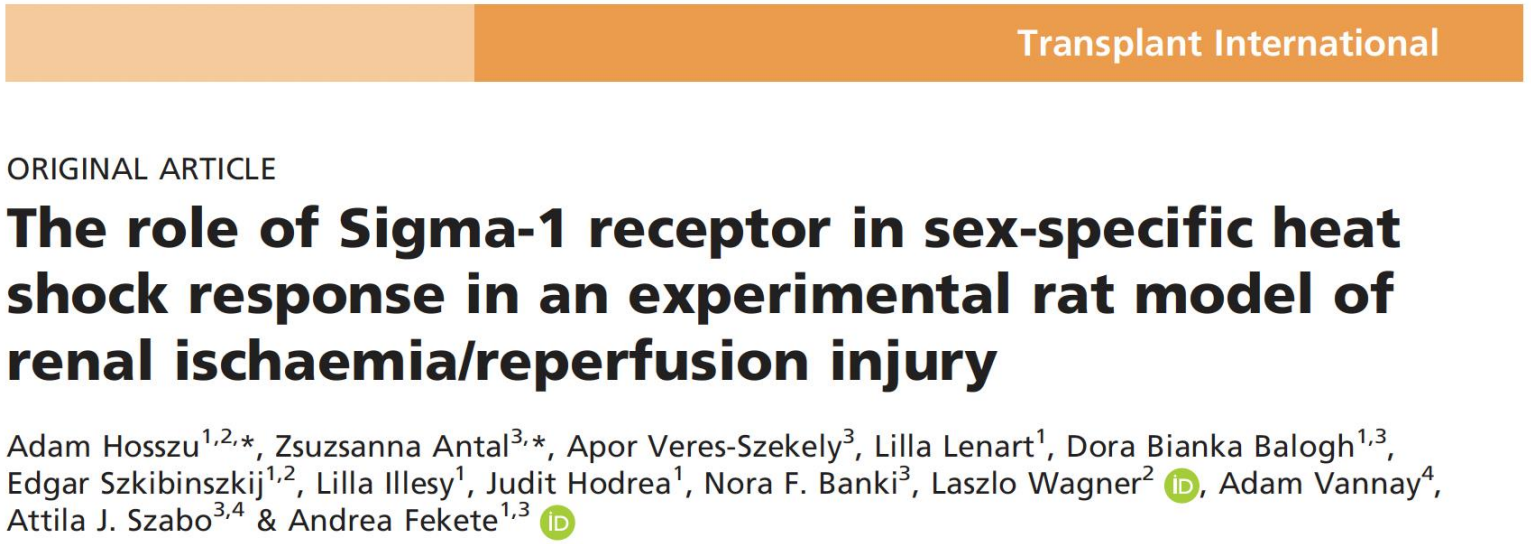


S1R activation alleviates ischemic injury by improving renal perfusion





THE S1R AND SEX DIFFERENCES IN RENAL IRI



Transplant International

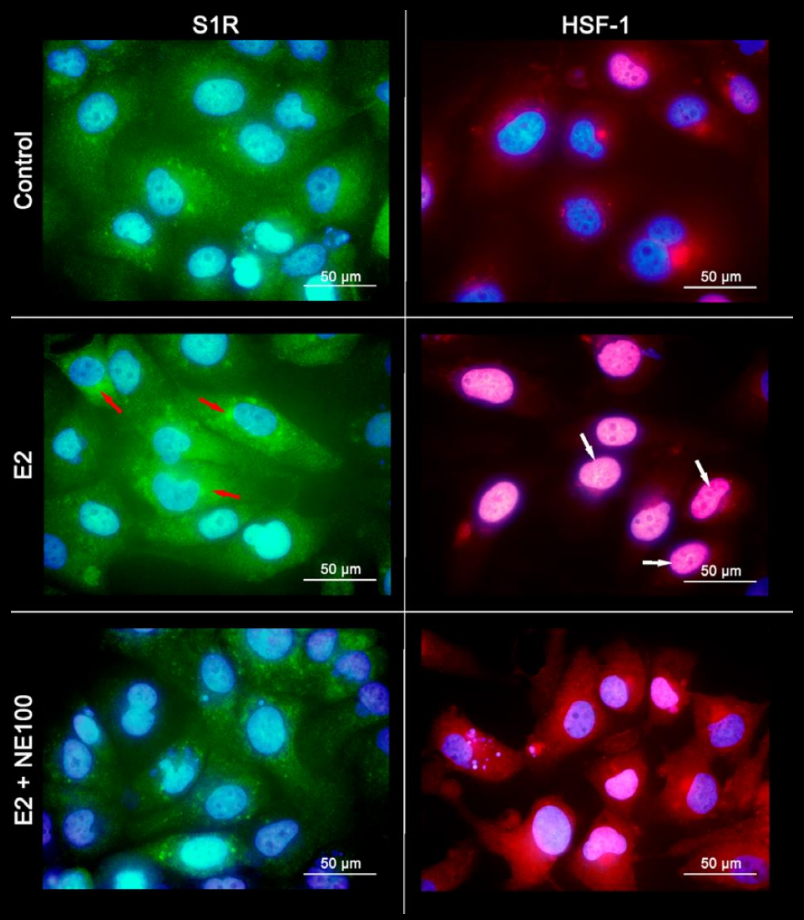
ORIGINAL ARTICLE

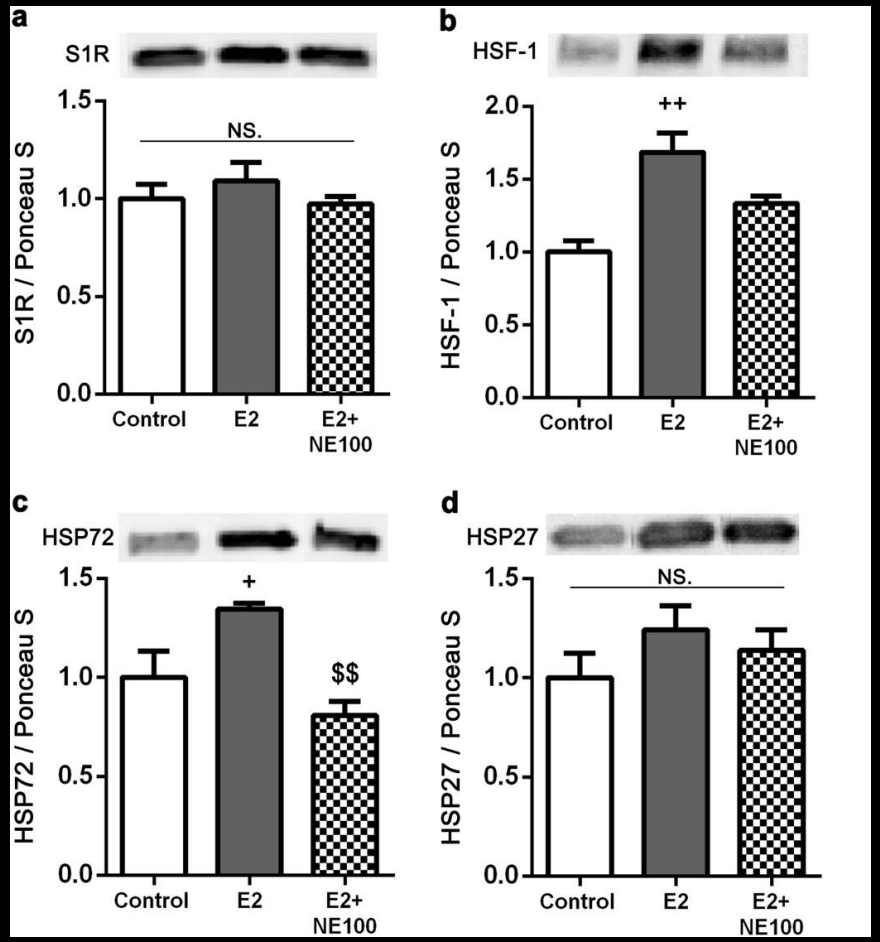
The role of Sigma-1 receptor in sex-specific heat shock response in an experimental rat model of renal ischaemia/reperfusion injury

Adam Hosszu[1,2,*], Zsuzsanna Antal[3,*], Apor Veres-Szekely[3], Lilla Lenart[1], Dora Bianka Balogh[1,3], Edgar Szkibinszkij[1,2], Lilla Illesy[1], Judit Hodrea[1], Nora F. Banki[3], Laszlo Wagner[2], Adam Vannay[4], Attila J. Szabo[3,4] & Andrea Fekete[1,3]

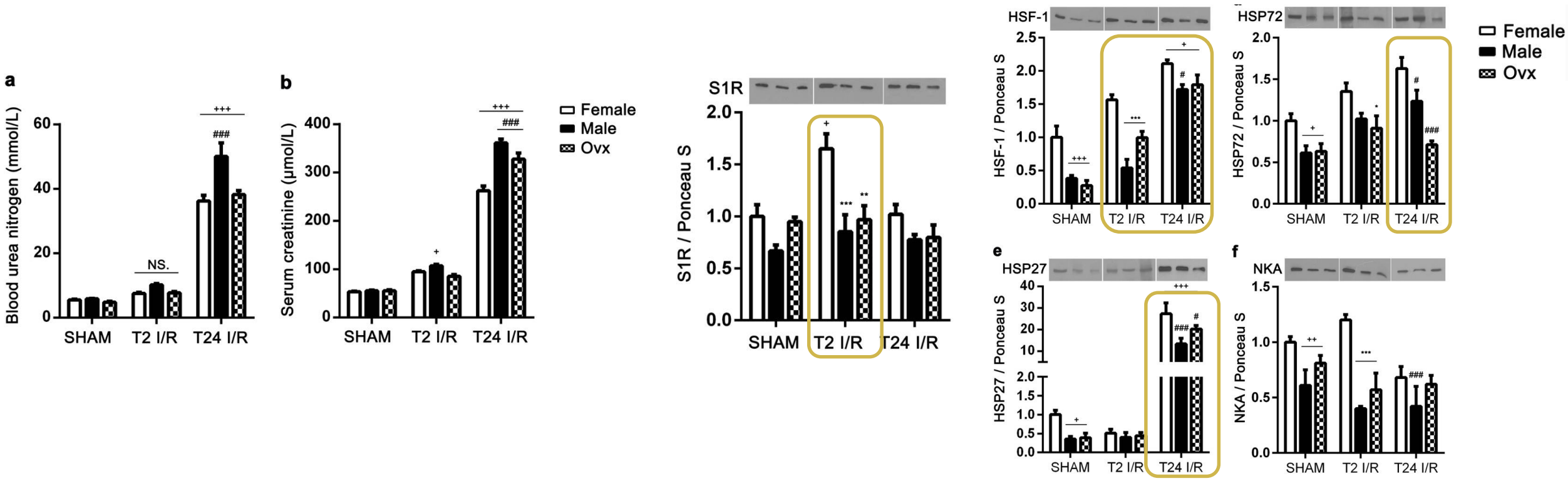
- Morbidity is higher in men than in women in many IRI-related diseases *(Fels JA. et al. 2019)*
- After menopause, the incidence of ischemic disease is similar in both sexes
- Males are more susceptible to renal IRI (*Fekete A. et al. 2004; Muller V. et al. 2002*)
- **Estrogen is an endogenous ligand of Sigma-1 receptor**

- **S1R and Heat Shock Factor-1 are activated by estrogen** in proximal tubular cells
- Estrogen induces HSF-1 and HSP-72 production





- Post-ischemic kidney function is better in female rats
- S1R protein levels rapidly increase in females after IRI
- Post-ischemic Heat Shock Protein and Na^+/K^+-ATP-ase protein levels are higher in females



THE S1R AND INNOVATION IN ORGAN PRESERVATION

International Journal of *Molecular Sciences*

MDPI

Article

The Sigma-1 Receptor Is a Novel Target for Improving Cold Preservation in Rodent Kidney Transplants

Adam Hosszu [1,2], Akos R. Toth [1,2], Tamas Lakat [1,2], Ganna Stepanova [3], Zsuzsanna Antal [2], Laszlo J. Wagner [4], Attila J. Szabo [2] and Andrea Fekete [1,2,*]

Compositions for organ preservation

Abstract

The invention relates to the field of preserving the viability of organs or tissues to be transplanted into a recipient in need of such a transplantation. In particular, the invention relates to use of a sigma 1 receptor agonist compound in preservation solutions and preservation solutions comprising a sigma 1 receptor agonist compound.

EP3544420A1
European Patent Office

Find Prior Art Similar

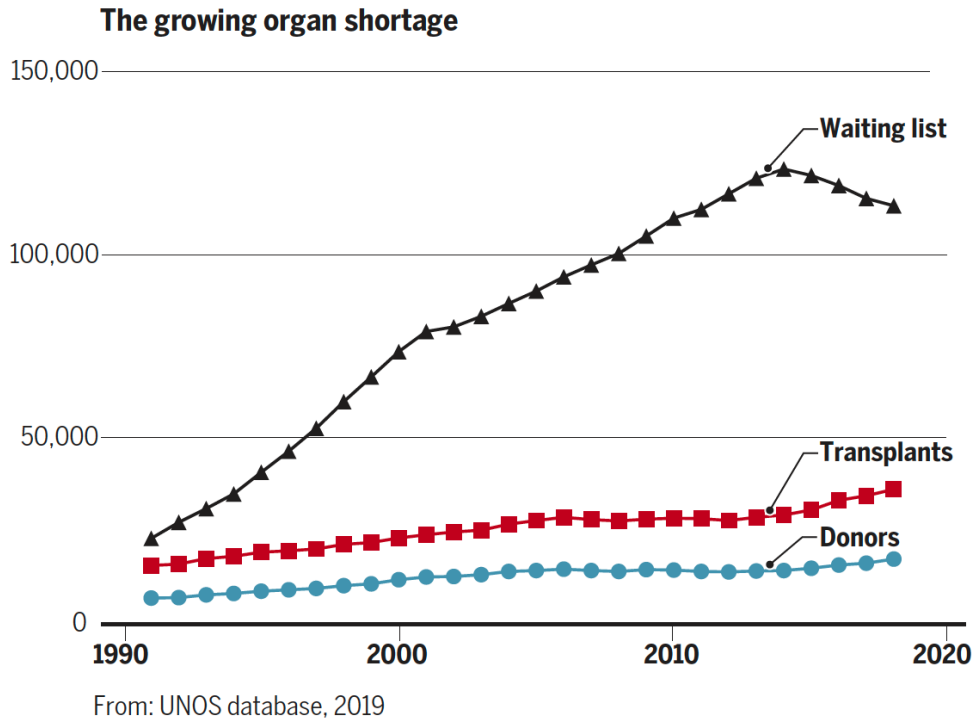
Other languages: German, French

Inventor: Andrea FEKETE, Ádám VANNAY, Ádám HOSSZÚ

The problem - organ shortage

AIM: To increase the number of organs suitable for transplantation:

- Optimization of graft quality
- Prolonging storage time by alleviating cold ischemic graft injury



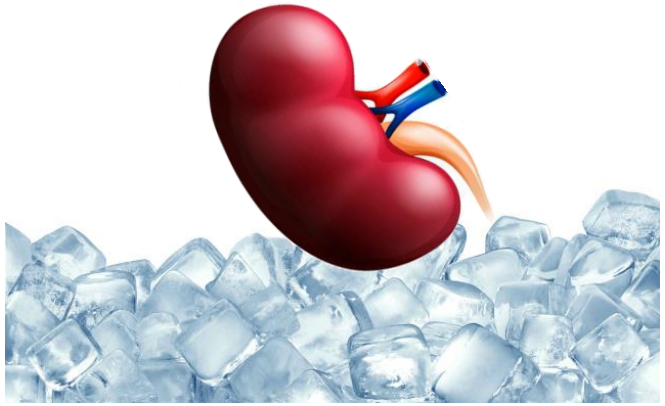
From: UNOS database, 2019

Methods

I.

- Kidney autotransplantation (ATx)
- Organs flushed with a S1R agonist

II.



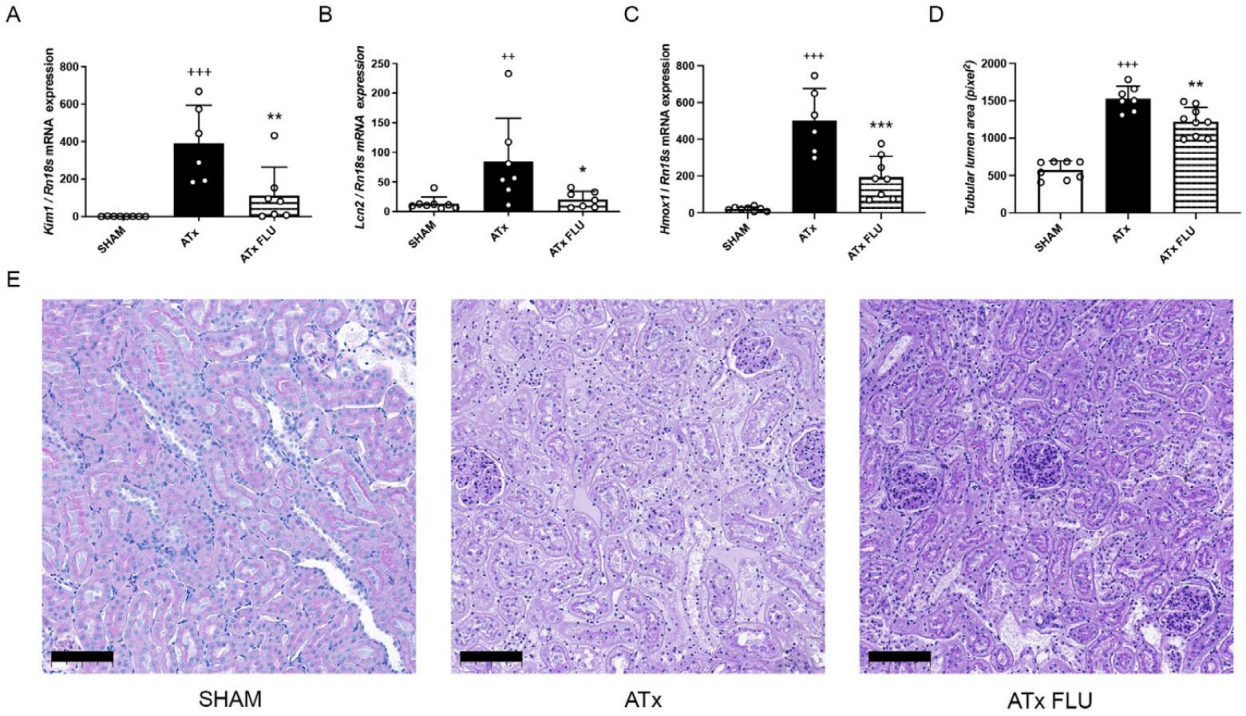
- Cold ischemia(CI)
- Organs flushed with a S1R agonist
- 2 / 24 h

S1R agonist FLU improves post-transplant kidney function and mitigates tubular injury

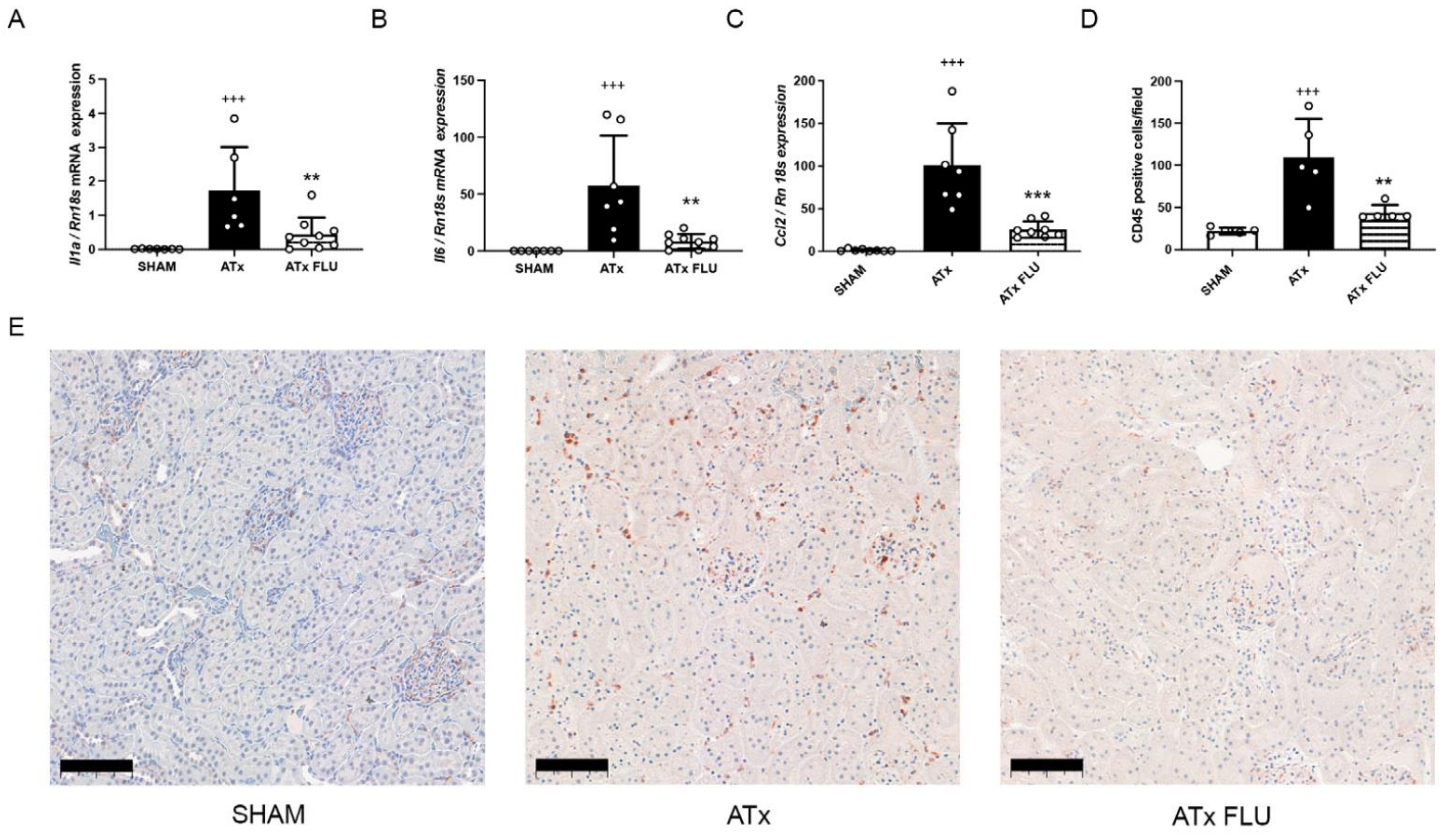
Table 1. Renal functional parameters are improved by fluvoxamine (FLU) following autotransplantation (ATx).

	SHAM	ATx	ATx FLU
Creatinine (µmol/L)	28.3 ± 6.2	361.7 ± 42 $^{+++}$	308.2 ± 42.6 $^{+++,*}$
BUN (mmol/L)	7.5 ± 1.8	55.5 ± 6.5 $^{+++}$	57 ± 7.7 $^{+++}$
AST (U/L)	233.8 ± 40	507.8 ± 180.8 $^{+++}$	294.3 ± 118.2 ***
Na (mmol/L)	142.8 ± 2.5	137.9 ± 3.1	137.2 ± 2.7
K (mmol/L)	6.9 ± 1	7.9 ± 0.8	8.2 ± 0.5
Cl (mmol/L)	103.2 ± 2.5	95.2 ± 4.1	93.2 ± 4.7

+++ $p < 0.001$ vs. SHAM, * $p < 0.05$; *** $p < 0.001$ vs. ATx, $n = 6–8$/group. BUN: blood urea nitrogen; AST: aspartate transaminase.



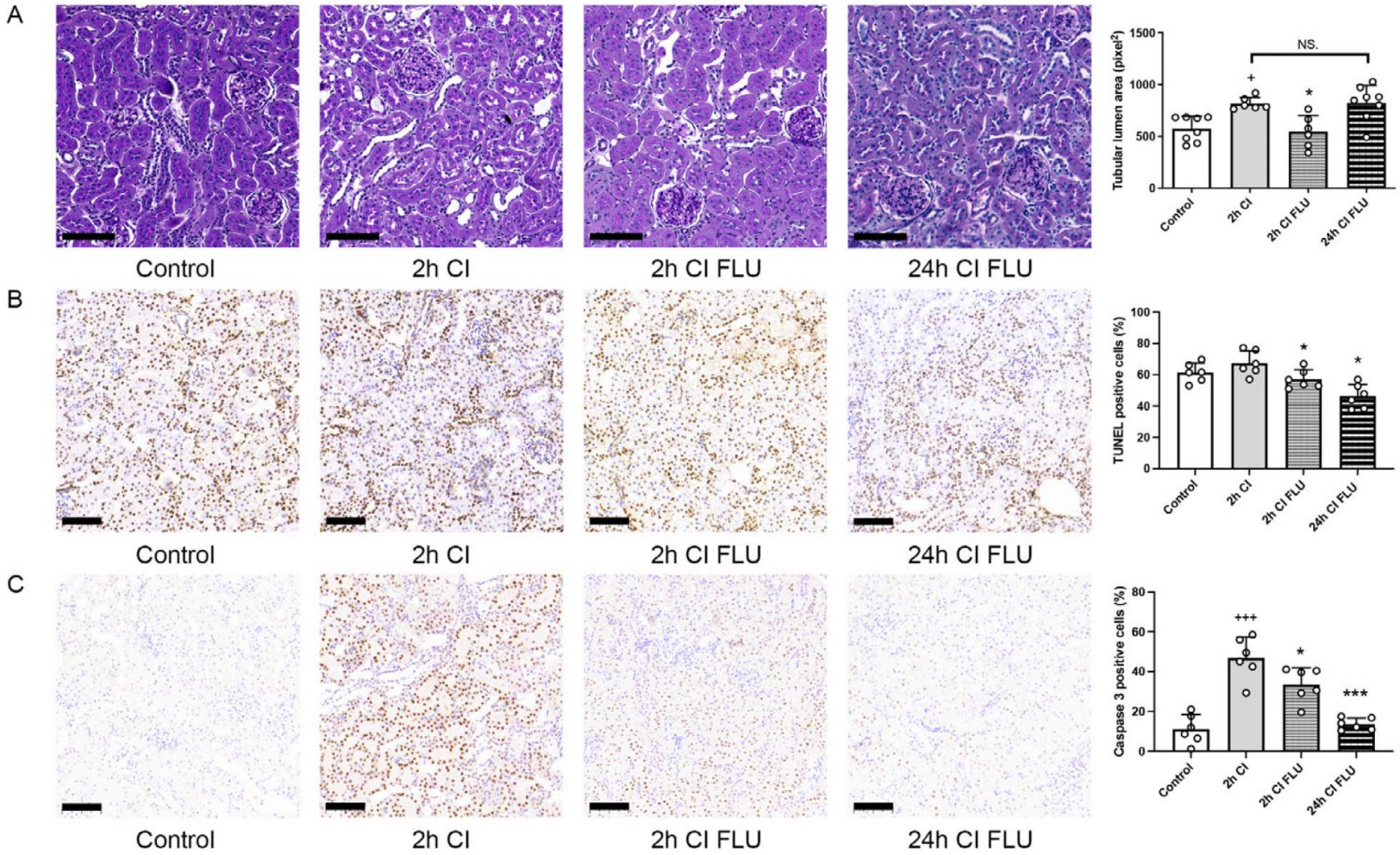
S1R agonist FLU alleviates inflammation in the kidney following ATx



Kidneys are better preserved during cold storage with the addition of S1R agonist

Structural injury

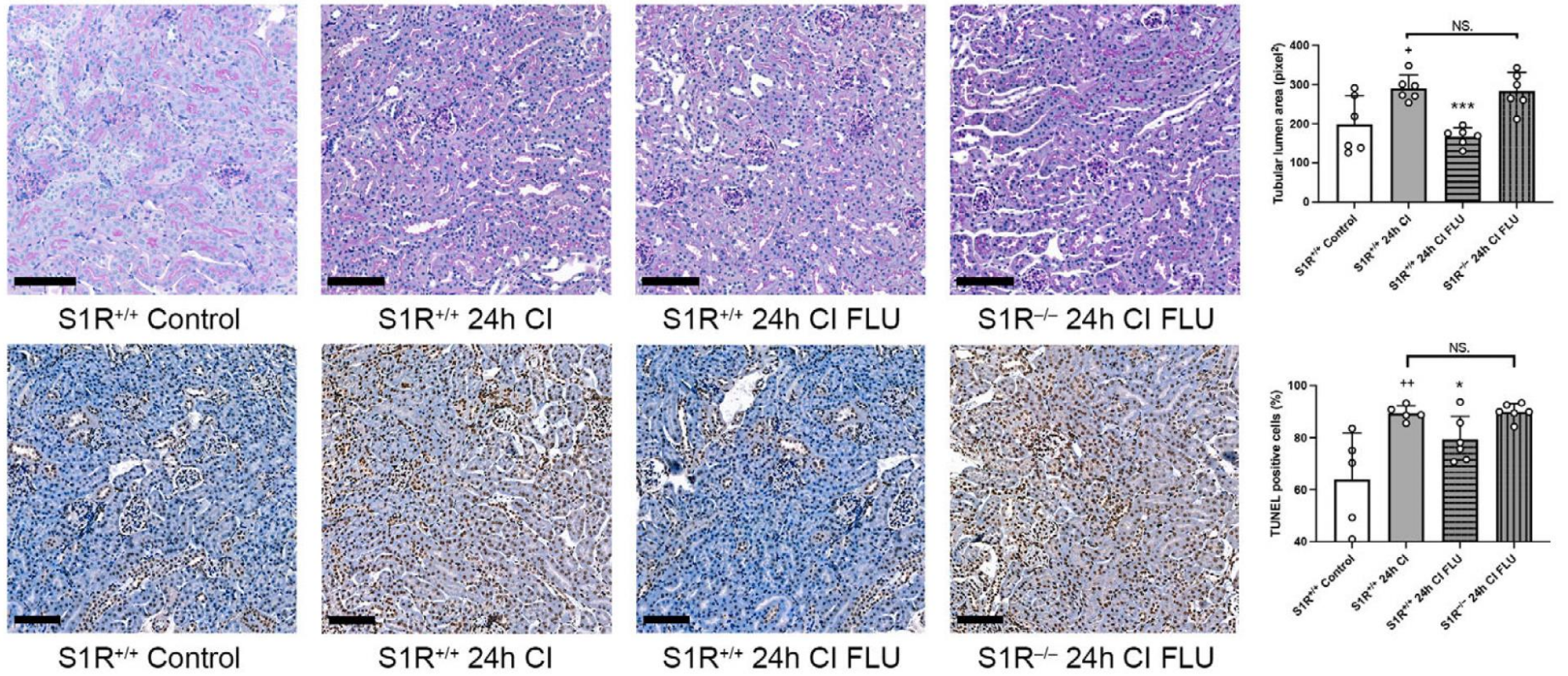
Apoptosis



The beneficial effects of S1R agonist FLU are diminished in S1R$^{-/-}$ mice

Structural injury

Apoptosis



SUMMARY

- S1R agonist treatment is protective in renal ischemic injury by improving perfusion in the kidney
- Estrogen – in part by activating S1R – induces a more pronounced heat shock response, which may be responsible for milder ischemic injury in females
- The addition of a S1R agonist to the preservation solution during transplantation improves graft function and alleviates injury
- S1R agonists reduce graft damage during cold storage thus, the number of transplantable organs can be increased

Thank you for your attention!

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