The effect of calcineurin-inhibition on the renal renin-angiotensin system. A new place for renin excretion.

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INTRODUCTION

- renal transplantation is the definitive therapy of end-stage renal failure
- Tacrolimus (Tac) and CyclosporinA (CyA) are two effective immunosuppressants which are essential therapeutic solutions in the prevention of allograft rejection
- it is well known that calcineurin inhibitors (CNIs) have nephrotoxic potential[1]
- it has been described that CNIs cause increased renin release in the JGA[2,3]
- in certain pathophysiologic conditions the principal cells in the collecting duct can regain the capability to produce renin[4,5]

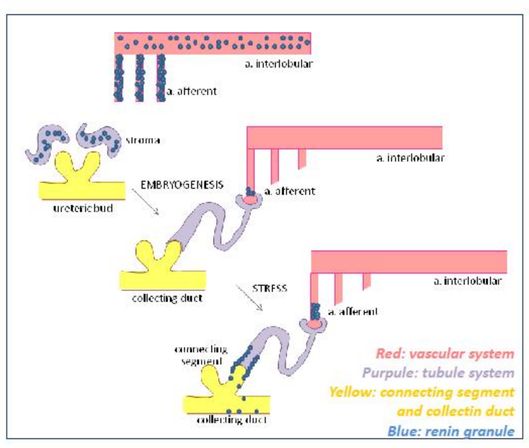

Figure 1. Embryogenesis and the impact of stress in terms of renin. In certain pathophysiologic conditions the principal cells in the collecting duct are able to regain the capability for renin production which was previously characteristic for the embryonic period. Doing so under stress conditions they initiate survival and profibrotic signals.

AIM

The precise mechanism of CNI-nephrotoxicty is still not fully revealed.

The aim of this study was to reveal whether the collecting duct has any role in the trigger and the maintenance of calcineurin inhibitor nephrotoxicity through the local renin production.

CONCLUSION

- our study revealed for the first time, that calcineurin inhibitors possess nephrotoxic effect on the kidney parenchyma due to the enhanced renin activity not only in the juxtaglomerular apparatus but also in the CD-s
- the inhibition of renin-angiotensin system by direct renin inhibitor could prevent these deteriorative effects
- inhibition of renin might serve as a therapeutic possibility in the prevention of calcineurin inhibitor nephrotoxicity in the future.
- further studies are needed to reveal what kind of inhibitors in which combination could provide the most efficient treatment

METHODS

- three weeks old, C57Black6 male mice
- three weeks of treatment:
  1. saline
  2. 0,075 mg/kg/day Tacrolimus (Tac)
  3. 2mg/kg/day Cyclosporin A (CyA)
  4. 0,075 mg/kg/day Tac + 25 mg/kg/nap Aliskiren (Tac+Alisk)
  5. 2mg/kg/day CyA + 25 mg/kg/day Aliskiren (CyA+Alisk)
- Multi-photon microscopy:
  - green: acidic organellum – renin (quinacrin)
  - red: vasculature (70kDa rhodamin dextran)
- Flow cytometry: AQP2+, renin+
- Histological analysis: blue – collagen (Masson staining)
- Renal functional parameter: serum creatinine

RESULTS

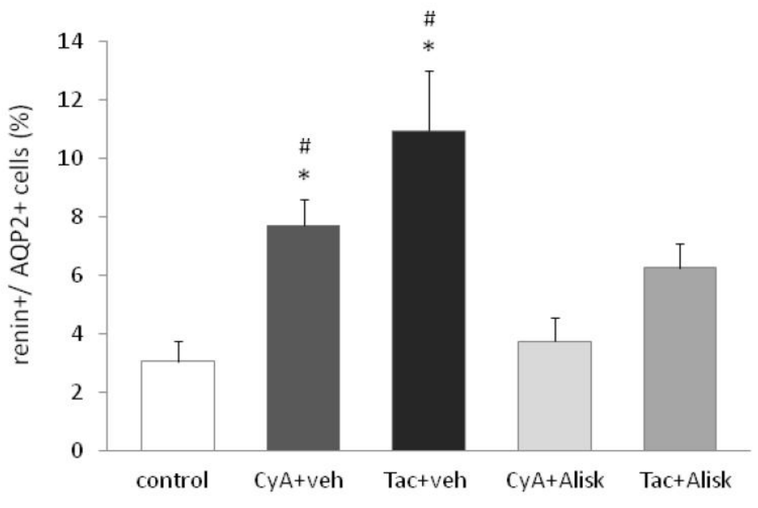

Figure 1. Renin content in the principal (AQP2+) cells, flow cytometry Control mice showed approximately 3% positivity for renin in the AQP2 positive principal cells. Following 3 weeks of CNI treatment we have seen a significant increase in renin content, which was reduced to the level of controls when the treatment was combined with the direct renin inhibitor Aliskiren. * p≤0.05 vs. control, # p≤ 0.05 vs. Aliskiren treatment; CyA: Cyclosporin A; Tac: Tacrolimus; Alisk: Aliskiren. n = 4-7 mice/group

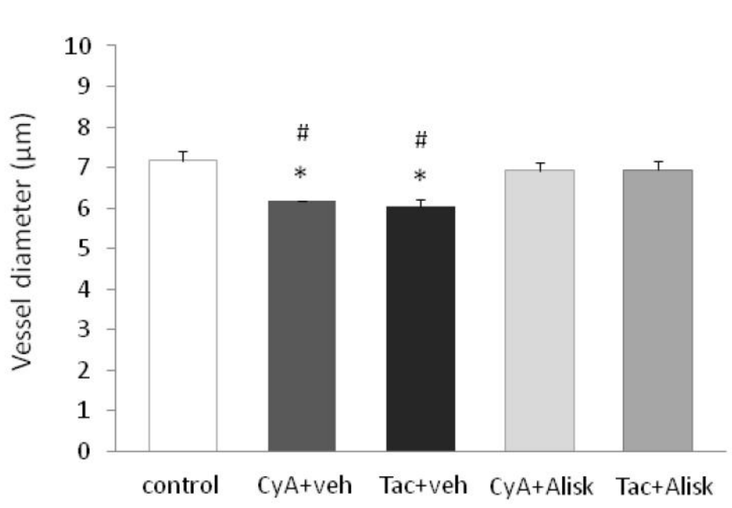

Figure 3. Diameter of peri-tubular capillaries, multi-photon microscopy Control mice had an avarage capillary diameter of 7.2±0.3µm. Following 3 weeks of CNI treatment the vessels showed significant contraction, which was abolished by co-treatment with direct renin inhibitor Aliskiren. * p≤0.05 vs. control, # p≤ 0.05 vs. Aliskiren treatment; CyA: Cyclosporin A; Tac: Tacrolimus; Alisk: Aliskiren n = 4-6 mice/group

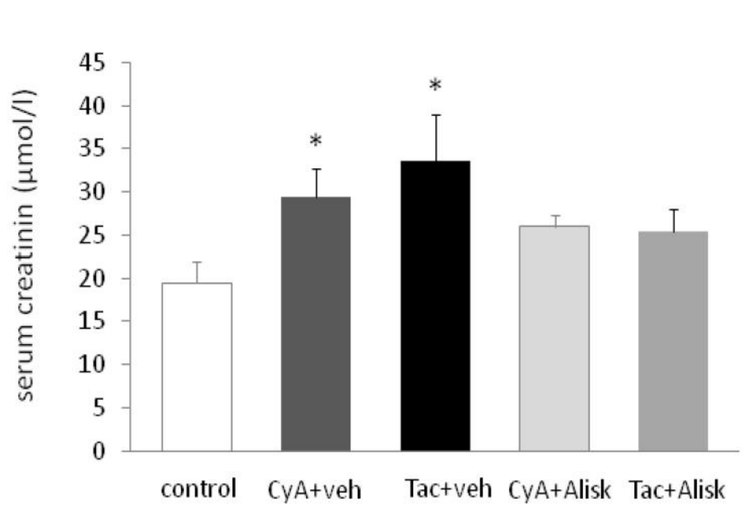

Figure 6. Renal function parameters, mass spectrometry In control mice the average creatinine values was 19.5±2.6 µmol/l, which increased significantly after 3 weeks of CNI administration. However, this elevation was abolished by the direct renin inhibitor Aliskiren. * p≤0.05 vs. control; CyA: Cyclosporin A; Tac: Tacrolimus; Alisk: Aliskiren. n = 4-6 mice/group

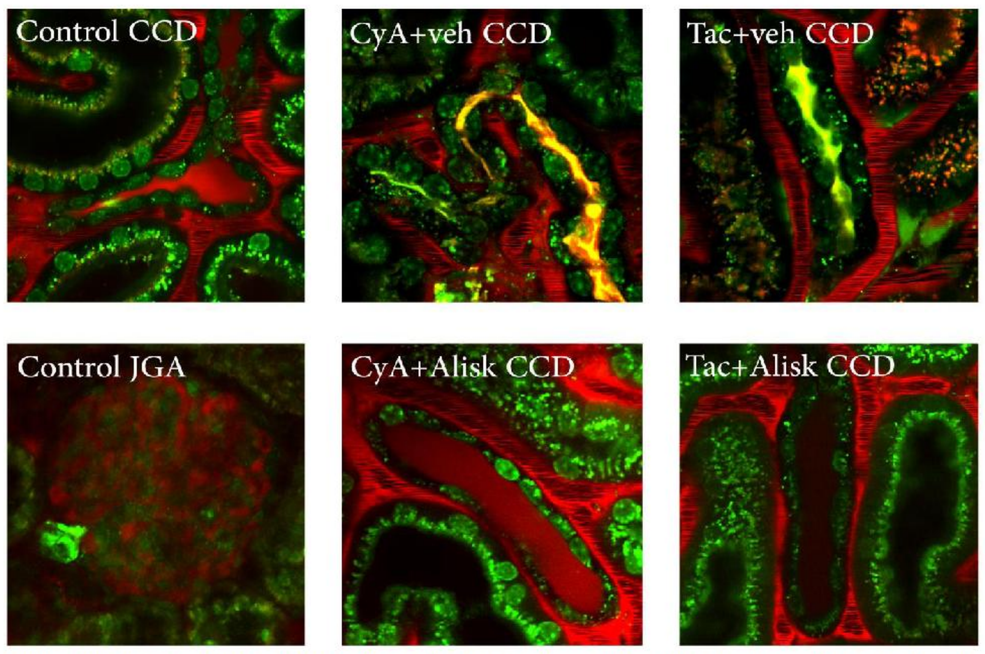

Figure 2. Renin content in the collecting duct, multi-photon microscopy The classical renin producing granular cells in the juxtaglomerular apparatus stained with quinacrin in green. The control group shows renin granules in trace, while the two CNI treated group presented robust expression of renin, which was almost completely abolished by the direct renin inhibitor Aliskiren. Green: quinacrin (renin positive granules), nuclei, autofluorescens; Red: 70kDa dextran (vasculature); CyA: Cyclosporin A; Tac: Tacrolimus; Alisk: Aliskiren. n = 4-6 mice/group

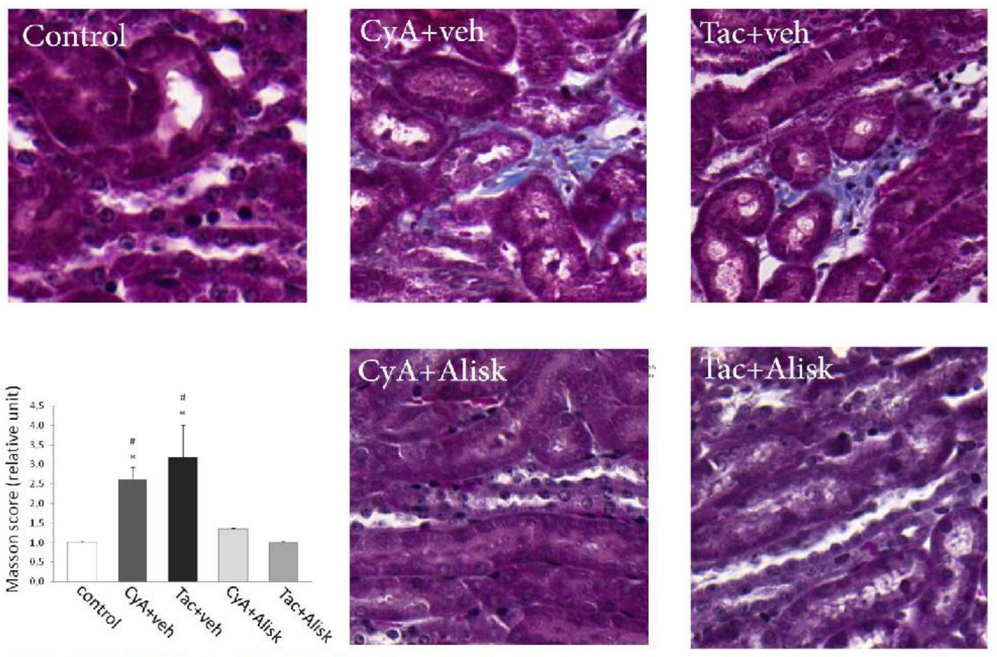

Figure 5. Striped fibrosis, Masson staining In controls there were some collagen staining around the arterioles, but hardly any interstitial staining was detected. However, 3 week CNI treatment resulted in significant fibrosis in both groups, mostly in the close proximity of collecting ducts. Administering direct renin inhibitor Aliskiren the amount of collagen reduced to the level of controls. Back: nuclei; Red: cytoplasm and erythrocytes; Blue: collagen. * p≤0.05 vs. control, # p≤ 0.05 vs. Aliskiren treatment; CyA: Cyclosporin A; Tac: Tacrolimus; Alisk: Aliskiren. n = 3 mice/group

References: [1]Remuzzi, Kidney Int Suppl. 1995;52:S70-4. [2] Madsen, Kidney Int.2010;77:110-117. [3] Andoh, SeminNephrol. 1997;17:34-45. [4]Gomez, Pediatr Nephrol, 1991;5(1):80-7. [5]Rohrwasser, Hypertension, 1999;34(6):1265-74.

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