ROLE OF PROSTAGLANDIN E_2 RECEPTOR EP_4 IN NEPHROTOXIC SERUM NEPHRITIS

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Background: The lipid molecule Prostaglandin E_2 (PGE_2) acts on four different receptors namely EP1-4. EP4 is expressed on different immune cells, resident kidney cells and endothelial cells. These cells play a crucial role in the pathophysiology of glomerulonephritis (GN). This study assessed the functional importance of EP4 receptor activation in experimental glomerulonephritis.

Method: To induce NTS, C57BL/6 mice were injected i.v. with rabbit anti-mouse glomerular basal membrane (GBM) serum. Starting from the day of GN induction mice were treated with an EP_4 receptor agonist [1000µg/kg and 280µg/KG BW], antagonist [5mg/kg BW] and vehicle (veh) s.c. twice daily. In vitro tubular cells were treated with an EP_4 receptor agonist and antagonist [1000nM-30nM].

Results:

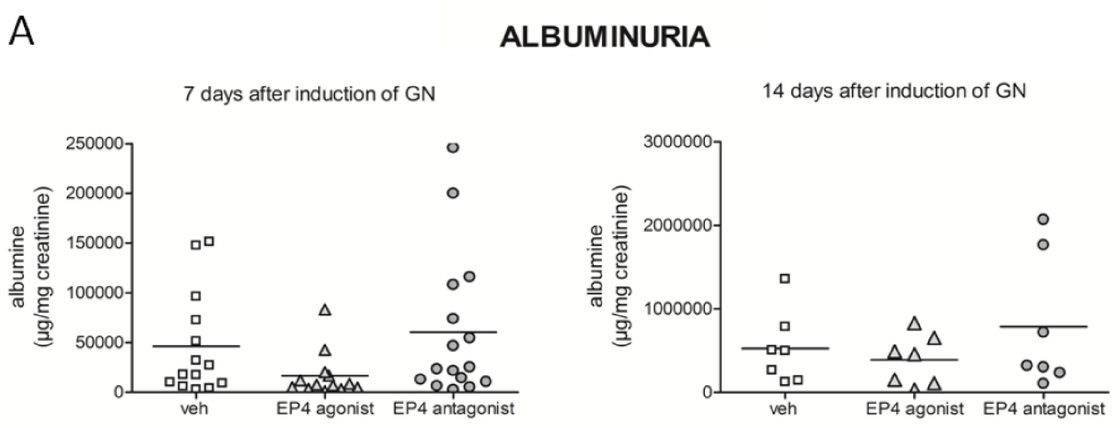

Fig. 1 – Albuminuria Day 7 and 14.
Urine samples collected on day 7 were alaysed for albumin and creatinine. Treatment with the EP4 receptor agonist showed a trend towards decreased albuminuria. Antagonist treated mice showed a trend towards increased albuminuria on day 14

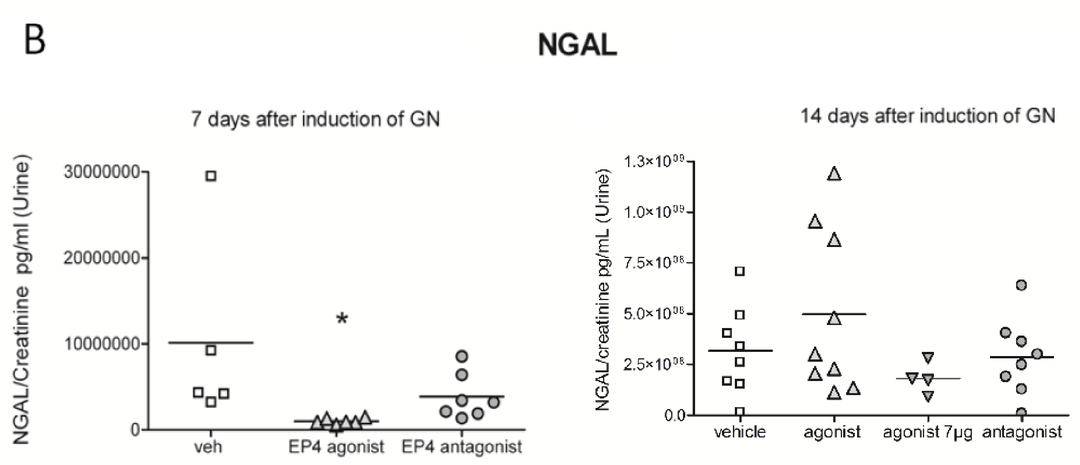

Fig. 2 –Agonist treated mice showed acute kidney injury. Mice treated with high dosages of the EP_4 receptor agonist displayed significantly increased acute tubular injury as depicted by increased urinary NGAL levels and increased tubular casts compared to the vehicle treated mice (p≤0,05).

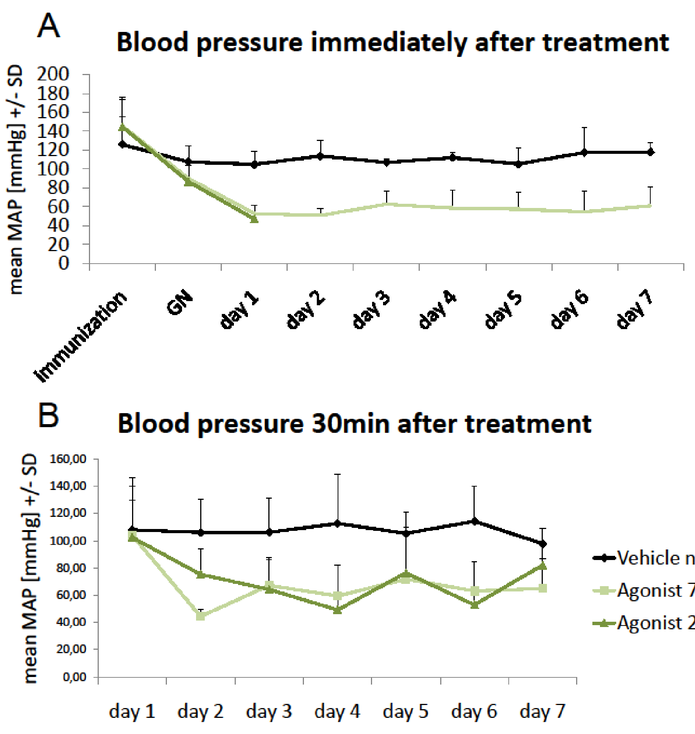

Fig. 3 – Hypotensive crisis after administration of the EP_4 receptor agonist. Mice treated with high and low dosages of the EP_4 receptor agonist showed recurrent hypotensive episodes after administration of the drug.

Fig. 4 Increased tubular injury in the high dosage agonist treated group. On day 14 the agonist (C) treated mice showed a significantly decreased PAS glomerular sclerosis score (D) compared to vehicle (A), and antagonist (C) treated mice. The high dosage agonist treated mice showed a significant increase of tubular casts on day 14 (E) (p≤ 0,05)..

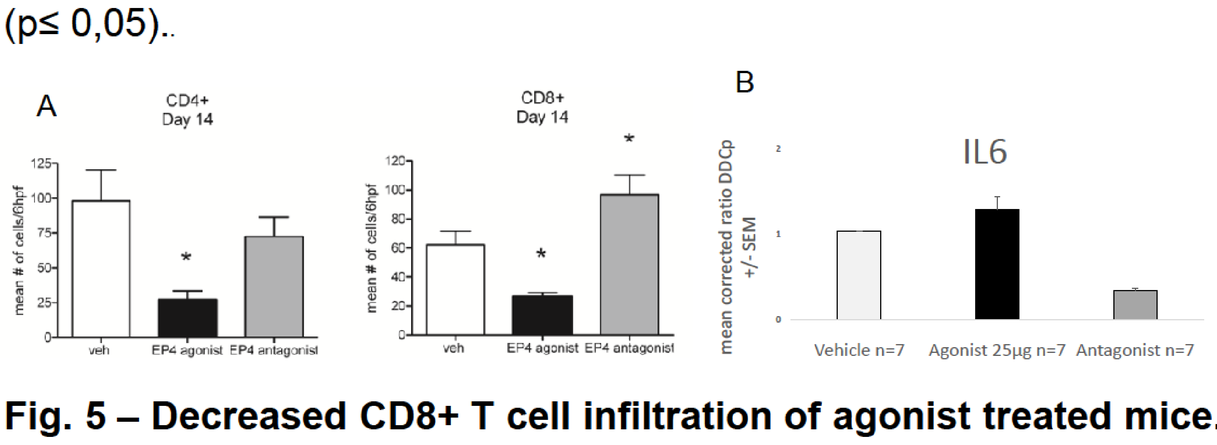

Fig. 5 – Decreased CD8+ T cell infiltration of agonist treated mice. The agonist treated mice showed a significant decreased CD8+ and CD4+ cell infiltration in the kidney (A) on day 14 (p≤ 0,05). Kindney IL6 expression was analysed via quantitativ realtime PCR (B). The antagonist treated mice showed significantly decreased renal IL6 mRNA expression (p≤0,05).

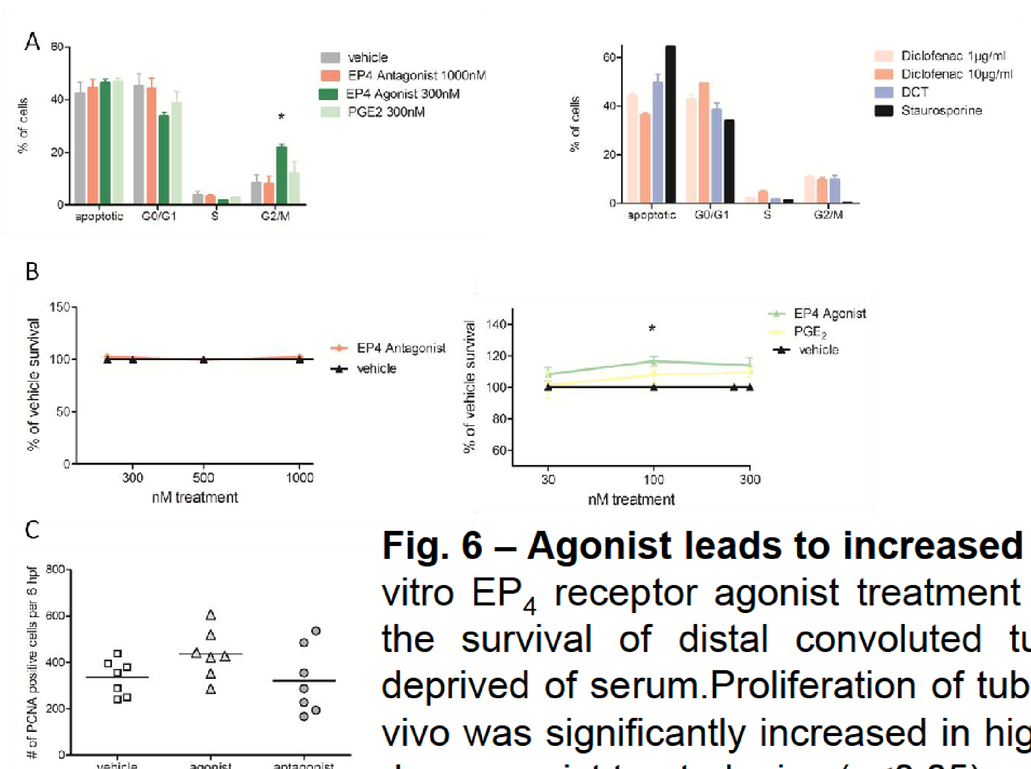

Fig. 6 – Agonist leads to increased viability. In vitro EP_4 receptor agonist treatment augmented the survival of distal convoluted tubular cells deprived of serum.Proliferation of tubular cells in vivo was significantly increased in high- and low-dose agonist treated mice (p≤0,05).

Conclusion: To sum up treatment with high-dosages of the EP_4 receptor agonist leads to an acute kidney failure, due to repeated low blood pressure because of vasodilation after administration of the drug. Agonist treated mice are having increased tubular casts, and a higher Lipocalin-2 level in the urine. Nevertheless they show decreased CD4+ and CD8+ cell infiltration into the kidney. In contrast, low-dose treatment is protective probably because of decreased infiltration of immune cells and an increased capacity of tubular cells to proliferate. Treatment with the EP4 receptor antagonist showed elevated CD8+ cell infiltration in the kidney, accompanied with a decreased renal IL6 mRNA expression.

MOLIN
FWF Der Wissenschaftsfonds.

All data are given as Mean +/- SEM