Fibroblast growth factor 23 modulates angiotensin receptor blockade in experimental renal fibrosis

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Introduction

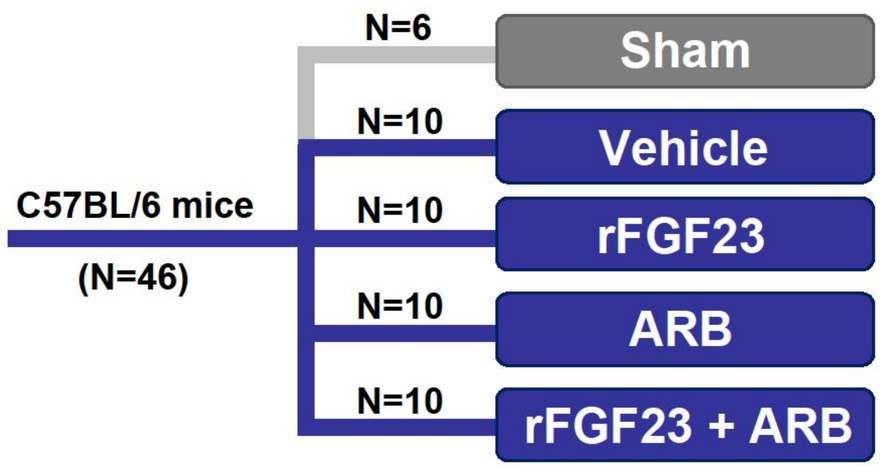
- The phosphaturic hormone Fibroblast growth factor 23 (FGF23) is strongly associated with both morbidity and mortality in CKD patients.
- It has been hypothesized that cross-talk between FGF23 and the the renin-angiotensin-aldosteron system (RAAS) may decrease the renoprotective effect of RAAS-blockade, thus contributing to treatment resistance and disease progression.

Aim

- To explore the interaction between FGF23 and RAAS-blockade efficacy in a mouse model of renal fibrosis.

Methods

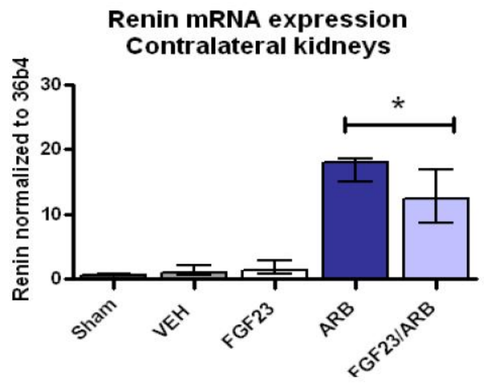
- Unilateral ureteral obstruction (UUO) mice were treated with mouse recombinant FGF23 (160ug/kg intraperitoneally twice daily) or vehicle, combined with either angiotensin receptor blockade (ARB; losartan, 100mg/L in drinking water) or vehicle, as shown below.

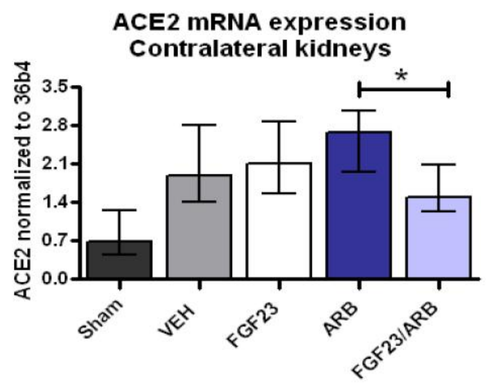


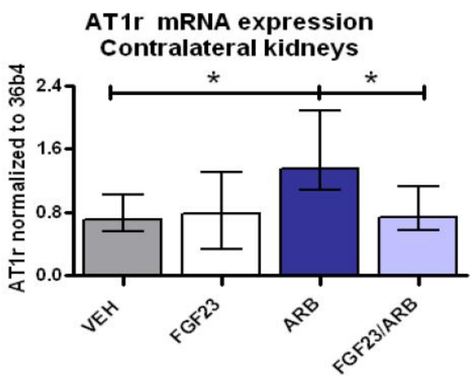
- Kidneys were collected 7 days after UUO surgery, and were analyzed using quantitative PCR.
- Contralateral kidneys were used to evaluate pharmacological interactions using the RAS-markers renin, angiotensin-converting enzyme (ACE), angiotensin-converting enzyme 2 (ACE2), and angiotensin II receptor type 1 (AT1r).
- The renoprotective efficacy of ARB treatment was analyzed in the injured kidneys using renal damage markers MCP-1, TNF-α, collagen-1, and lipocalin-2 (NGAL).
- Statistics were performed using nonparametric methods.
- All data is shown as Median [IQR].

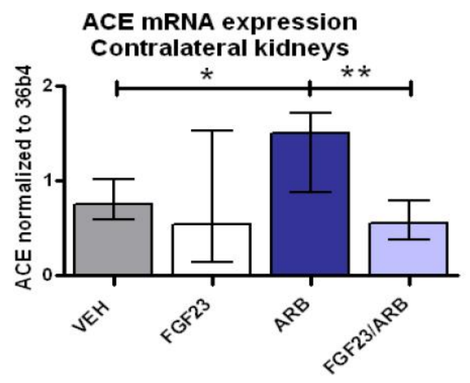
Results

Interaction between FGF23 and the RAAS

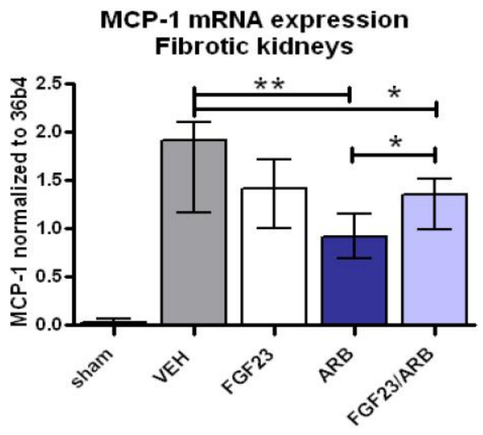


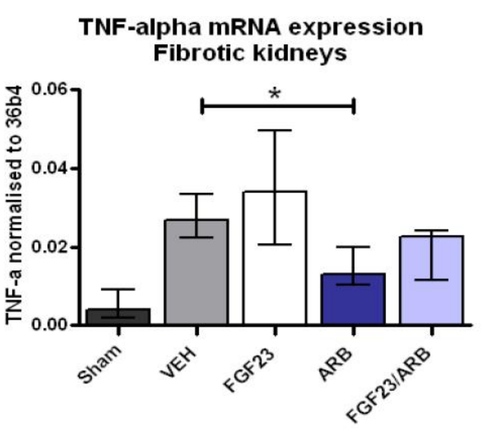


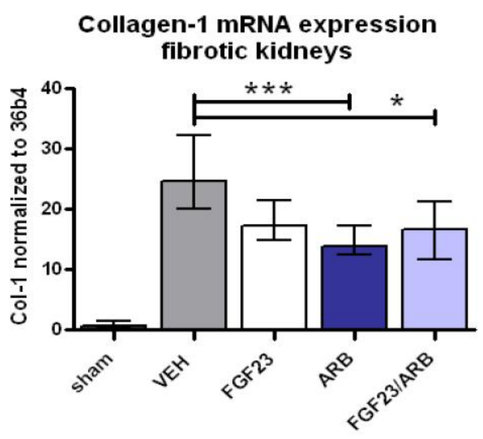


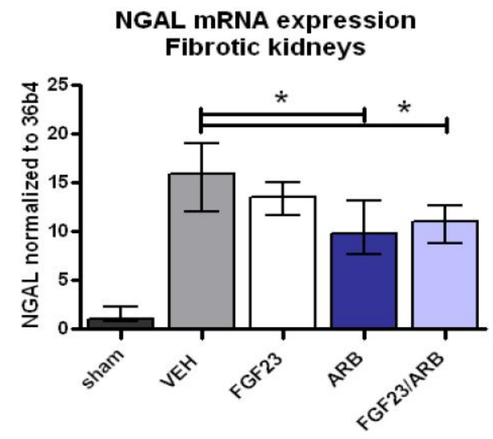


Effect of FGF23 on renoprotective efficacy

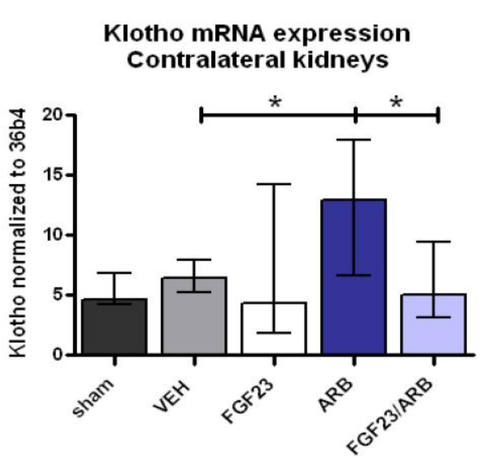


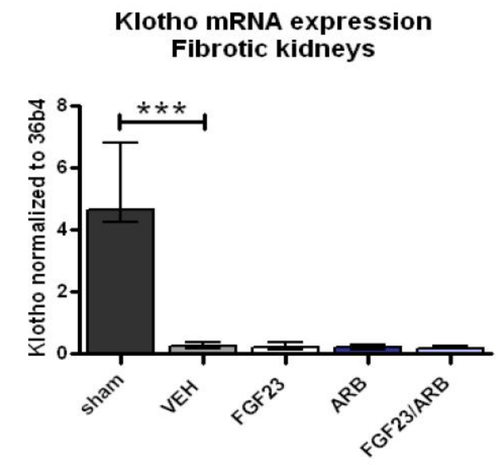






Expression of obligatory co-factor α-Klotho





Conclusions

In the UUO model of renal fibrosis, co-treatment with FGF23 modified the pharmacological effects of angiotensin receptor blockade. However, this interaction did not result in significant impediment of the renoprotective efficacy.

Possibly, severe downregulation of FGF23's obligatory co-factor α-Klotho in the injured kidneys may have limited any potentially harmful effects of FGF23.

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