Impact of Conditional Deletion of ADAM17 in Microglia on Kidney Fibrosis in Salt – Sensitive Hypertension

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Introduction

- Our lab previously demonstrated that microglial ADAM17 (A disintegrin and metalloprotease 17) plays a role in regulating salt-sensitive hypertension and the associated inflammatory response.
- More recently, we observed that deletion of ADAM17 from microglia mitigates neuronal hyperactivity and sympatho-excitation in salt-sensitive hypertension.
- The brain renin-angiotensin system (RAS) can exacerbate sympathetic activity to the kidney, further promoting sodium and water retention.
- However, the extent of microglia-kidney communication remains unclear.

Objective

- Our aim is to investigate the impact of ADAM17 deletion in microglia on renal sympathetic activity associated kidney fibrosis in salt-sensitive hypertension.

ADAM17 deletion in microglia alters the kidney size in salt sensitive hypertension

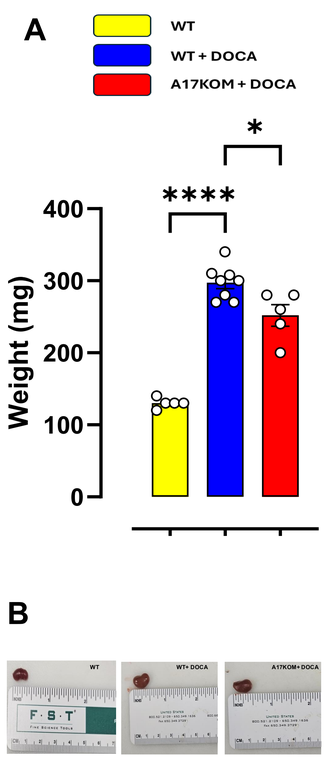

Figure 1: Weight of kidneys for all groups (**A**). Representative pictures of kidneys from all groups (**B**). Kidney size for all groups. The wild type (WT) + DOCA-salt kidneys appear large and inflamed, possibly related to excessive water/sodium retention. Mice lacking ADAM17 on microglia (ADAM17KOM) treated with DOCA-salt show reduced kidney size. These data suggest that ADAM17 in microglia might contribute to kidney inflammation in salt-sensitive hypertension. One-way ANOVA, Bonferroni post hoc test: (****P<0.0001 and *P<0.05).

Results

ADAM17 deletion in microglia attenuates kidney fibrosis in salt-sensitive hypertension

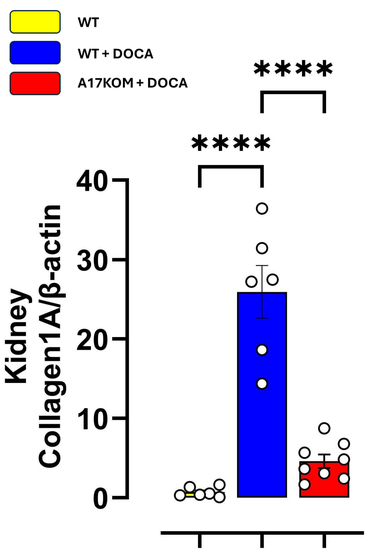

Figure 2: mRNA levels of collagen 1A expression in all groups. The WT + DOCA had significantly more collagen 1A expression than the ADAM17KOM + DOCA and the WT. It indicates that deletion of ADAM17 in microglia attenuates the kidney fibrosis in salt-sensitive hypertension. One-way ANOVA, Bonferroni post hoc test: (****P<0.0001).

Collagen 1A deposition in kidney glomeruli

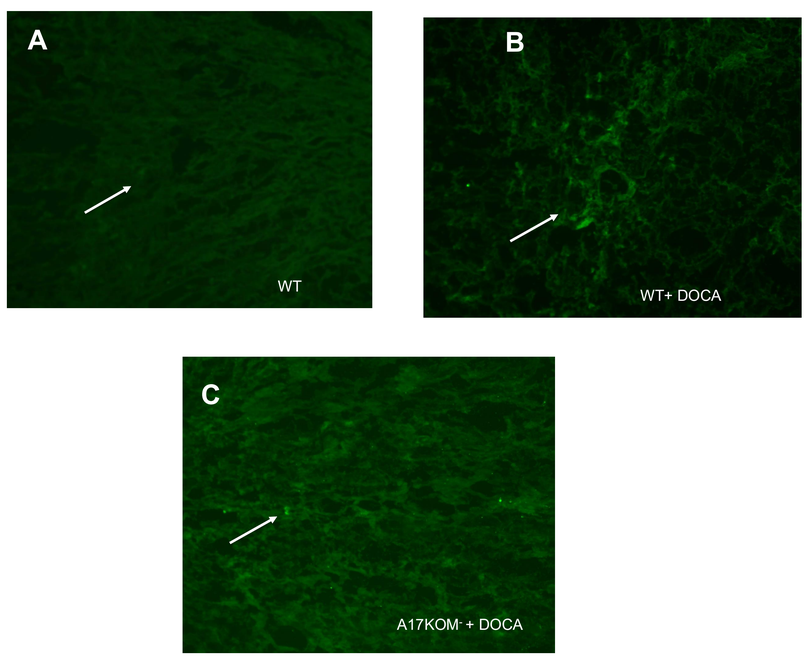

Figure 3: Fibrosis was assessed by measuring glomeruli collagen deposition. Representative immunofluorescence images of collagen1 (**A**) in kidney sections (glomeruli region). The dark green dots represent the deposition of Collagen 1A in glomeruli (**B**). The WT and ADAM17KOM with DOCA show less deposition of collagen1A (**A** and **C**). 10X magnification. These data suggest that the deletion of ADAM17 in microglia hampers the deposition of collagen 1A in kidney in salt – sensitive hypertension.

Interplay between the sympathetic nervous system and the kidney's renin-angiotensin system (RAS)

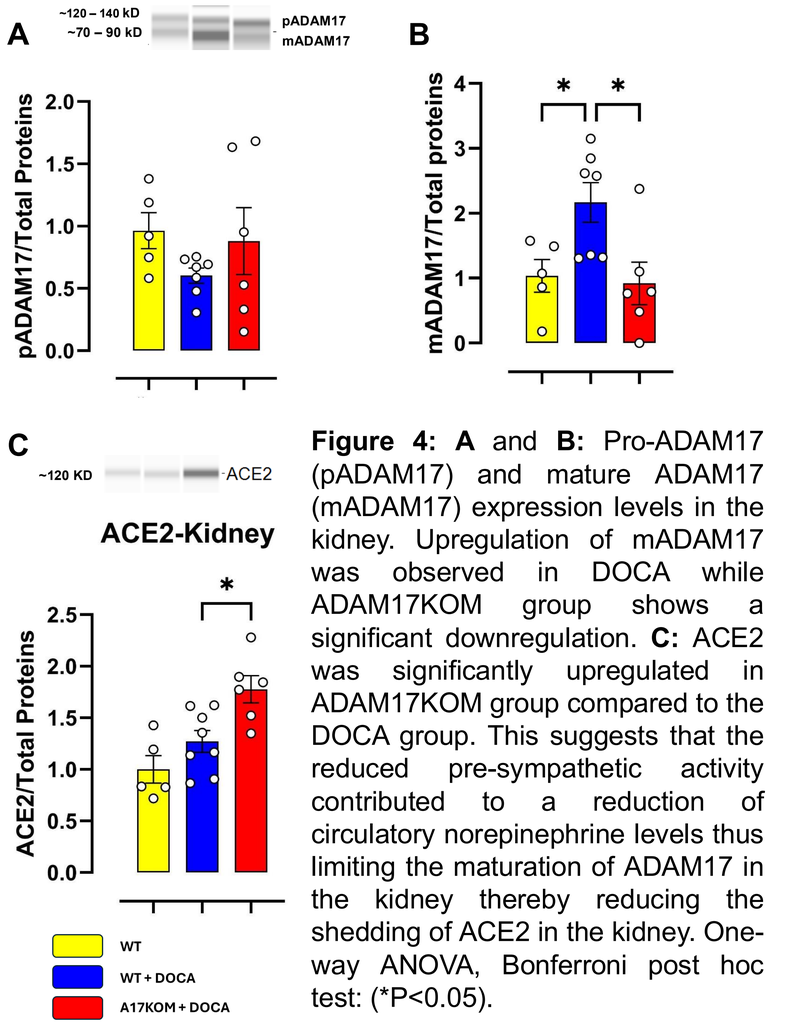

Figure 4: A and **B:** Pro-ADAM17 (pADAM17) and mature ADAM17 (mADAM17) expression levels in the kidney. Upregulation of mADAM17 was observed in DOCA while ADAM17KOM group shows a significant downregulation. **C:** ACE2 was significantly upregulated in ADAM17KOM group compared to the DOCA group. This suggests that the reduced pre-sympathetic activity contributed to a reduction of circulatory norepinephrine levels thus limiting the maturation of ADAM17 in the kidney thereby reducing the shedding of ACE2 in the kidney. One-way ANOVA, Bonferroni post hoc test: (*P<0.05).

Conclusion

- There is a significant decrease in collagen 1A expression when ADAM17 is conditionally deleted from microglia.
- Additionally, when ADAM17 is removed from microglia, there is significantly more ACE2 expression and significantly less mADAM17 in the kidney compared to the WT when they are both given the DOCA treatment.
- Thus, we conclude that ADAM17 in microglia play a role in kidney fibrosis in salt sensitive hypertension.