SUPPLEMENTAL MATERIAL

Figure S1.

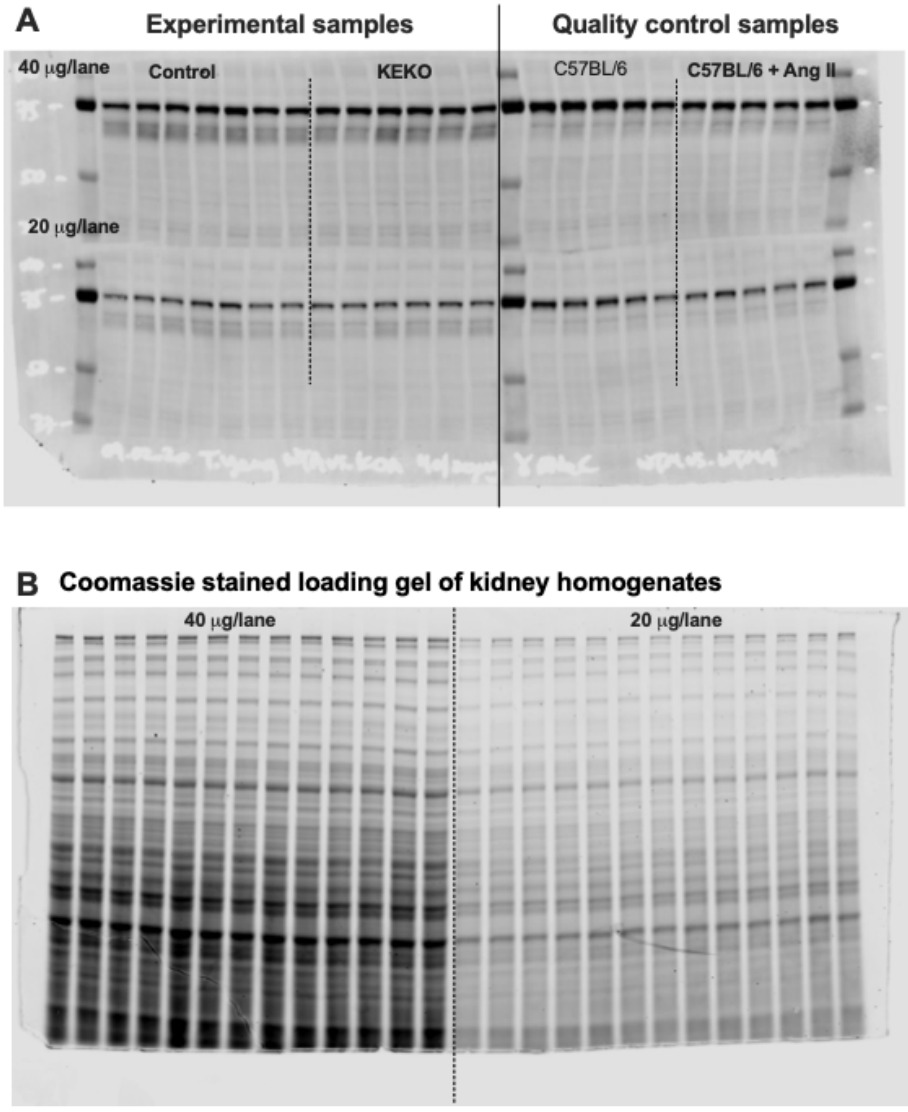

Figure S1. Determine linearity of the western blot detection system and Coomassie gel stain. (A) 1 (40 μg/lane) and ½ amounts (20 μg/lane) of protein from experimental samples (Control & KEKO) and additional wild-type mice with/without Ang II infusion (WT Control & WT Ang II) were assayed to verify the linearity of the detection system. (B) Representative picture of the coomassie gel stain.

Figure S2.

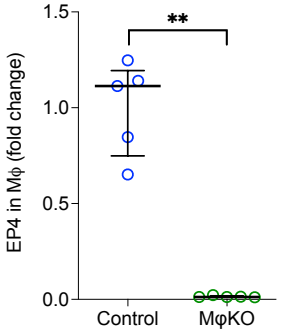

Figure S2. EP4R deletion verification in MϕKO mice. EP4 mRNA expression was significantly reduced in primary inactivated peritoneal macrophages from MϕKO mice. Data are expressed as mean ± SEM and analyzed by unpaired t tests; ** p<0.01 (effect size: large); n=5/group.

Figure S3.

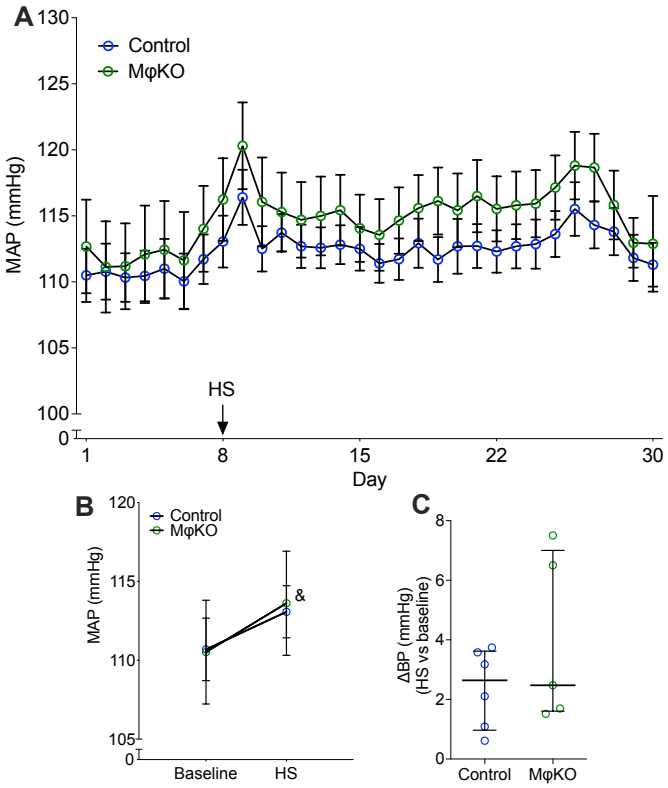

Figure S3. Mice lacking EP4R in macrophages maintained normal blood pressure response to prolonged high salt treatment. MAP was measured by telemetry at baseline and during 3 weeks of high salt feeding. The MϕKOs have similar blood pressure changes in response to 3 weeks of high salt feeding **(A)**. The blood pressure from baseline to high salt feeding was significantly elevated in MϕKOs **(B)**. The blood pressure

change from baseline to high salt feeding was maintained at a similar level in Control and MϕKOs **(C)**. Data are expressed as mean ± SEM for panel A, or median with interquartile range for panels B & C; panels A & B are analyzed by two-way ANOVA with Sidak multiple comparisons tests; panel C is analyzed by Mann-Whitney test; & $p<0.05$, MϕKOs HS vs MϕKOs baseline (effect size: small); MAP: mean arterial pressure; HS: high salt.

Figure S4.

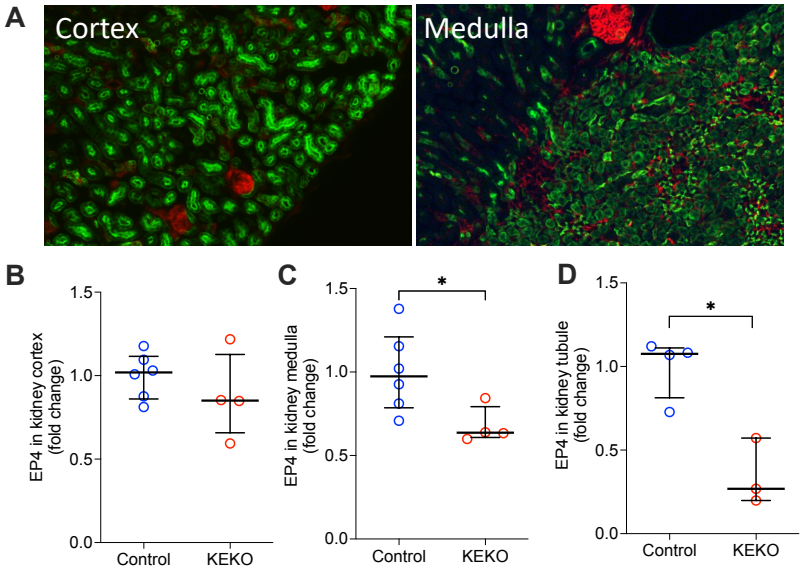

Figure S4. Verification of kidney epithelial cells- specific *Cre* expression and EP4 deletion in KEKO mice. (**A**) Cre expression in kidney cortex and medulla from *mTmG/Pax8-rtTA*$^{+}$*/TetO-Cre*$^{+}$ mice. Green fluorescent indicates *Cre* expression. (**B**) EP4 mRNA expression in the kidney cortex. (**C**) EP4 mRNA expression in kidney medulla. (**D**) EP4 mRNA expression in enriched kidney tubule. Data are expressed as median with interquartile range and analyzed by Mann-Whitney test; * $p<0.05$ (effect size: large, respectively); n=4-6/group for panels B-C, n=3-4/group for panel D.

Figure S5

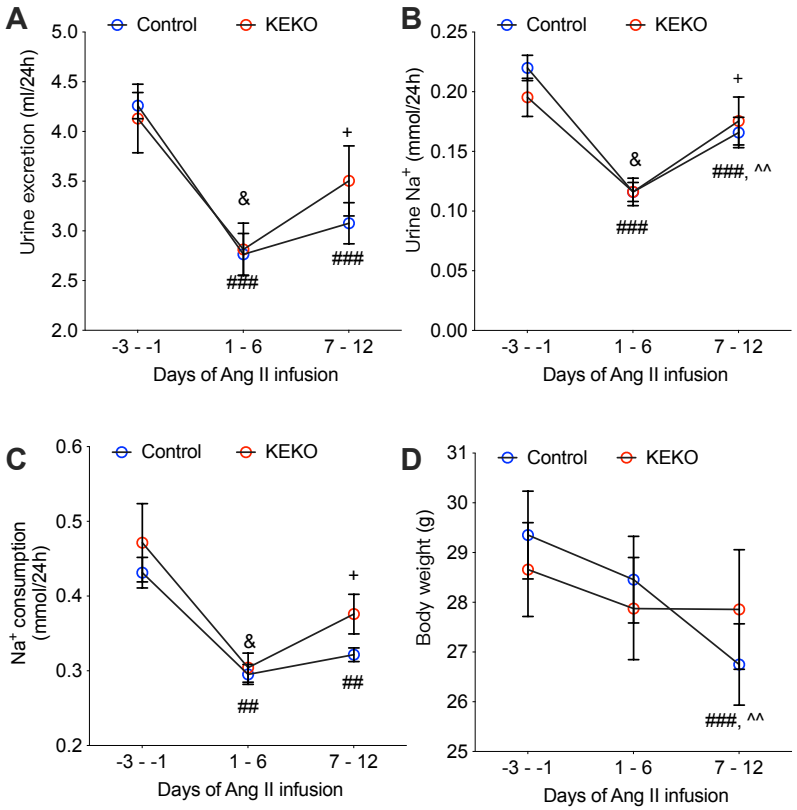

Figure S5. The sodium balance study. Mice were individually placed in metabolic cages. After 2 days of calibration, 24h urine was collected daily at baseline for 3 days and during Ang II infusion (1000 mg/kg/min) for 12 days. We did not observe significant statistical differences in urine excretion (A), urine sodium excretion (B), sodium consumption (C), and body weight (D) between Control and KEKO mice before and during Ang II infusion. Data are expressed as mean ± SEM and analyzed by two-way ANOVA (factors: genotype and days) with Sidak multiple comparisons tests; ## $p<0.01$, ### $p<0.001$ vs Control baseline; ^^ $p<0.01$ vs Control Ang II days 1-6; & $p<0.05$ vs KEKO baseline; + $p<0.05$ vs KEKO Ang II days 1-6; (effect size: medium – large for panel A, large for panel B & C, small for panel D); n=7-8/group.

Figure S6.

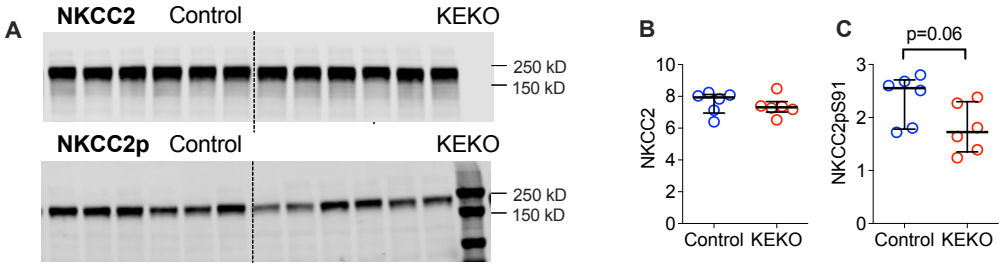

Figure S6. The NKCC2 abundance during Ang II-HTN. Protein was extracted from whole kidneys from Contol and REKO mice after 14 days of Ang II infusion. No differences in levels of total or phosphorylated NKCC2 proteins were detected. (**A**) Gel images of western blotting for NKCC2 and NKCC2p. (**B-C**) Quantification of the western blotting for NKCC2 and NKCC2p. Data are expressed as median with interquartile range and analyzed by Mann-Whitney test; n= 7 & 6/group; NKCC2: Na-K-2Cl cotransporter.

Figure S7.

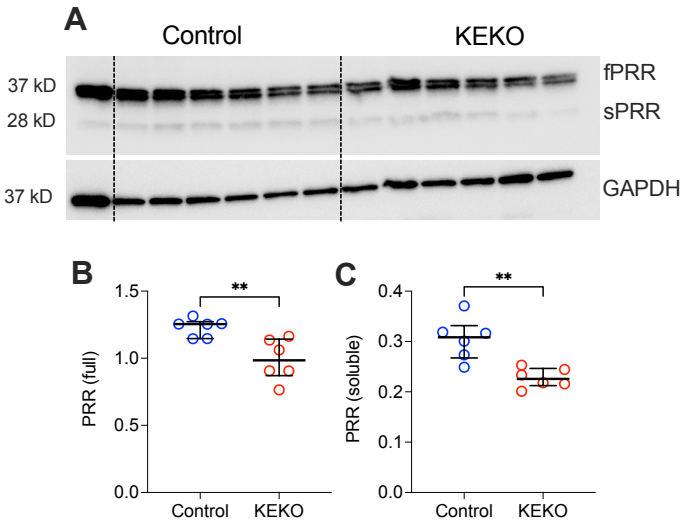

Figure S7. PRR is reduced in KEKO mice in hypertension. Protein was extracted from the kidney medulla after 4 weeks of Ang II infusion. (**A**) Gel images of western blotting for PRR, the first sample is positive Control. KEKOs have a significantly lower full length (**B**) and soluble (**C**) PRR expression in the kidney medulla compared to Controls. Data are expressed as median with interquartile range and analyzed by Mann-Whitney test; ** p< 0.01 (effect size: large); n= 6/group; PRR: (pro) renin receptor.