Glucocorticoid Receptor Signaling in the Distal Convoluted Tubule of the Kidney and Circadian Blood Pressure Control

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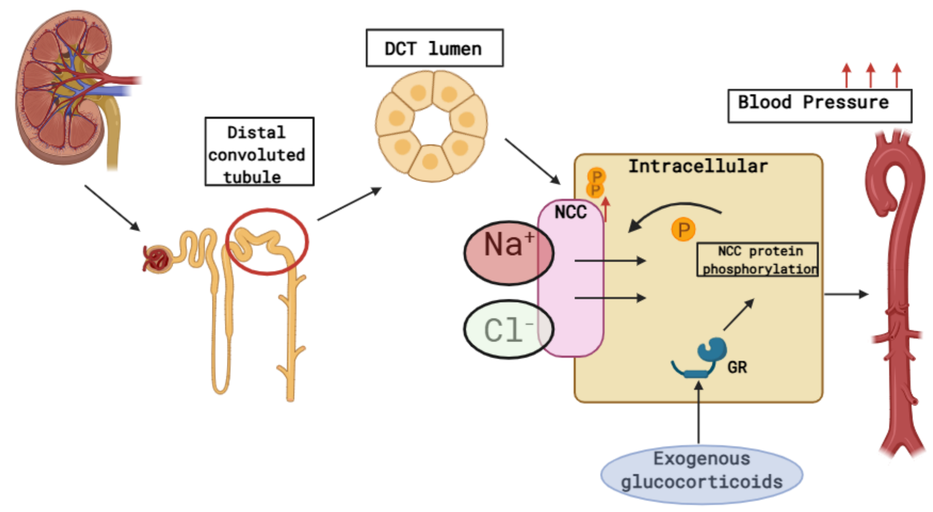
Introduction

- Exogenous glucocorticoids, widely used in clinical therapies (e.g. anti-inflammatory), can lead to the development of hypertension, by increasing sodium retention and blunting normal circadian blood pressure rhythms (1).
- The glucocorticoid receptor (GR) in the distal convoluted tubule (DCT) in the kidney is a key mediator of this effect, as it has been shown that GR activation promotes phosphorylation of the sodium chloride cotransporter (NCC), particularly during the active phase (see Fig 1) (2). GR knockdown was shown to disrupt normal diurnal rhythm of NCC activity. This loss of rhythm contributes towards a 'non-dipping' blood pressure profile – a clinical pattern which is associated with an increased cardiovascular risk (2).
- Specifically targeting GR in the DCT may offer a novel approach towards preventing glucocorticoid-induced hypertension, by preserving circadian sodium handling and protecting the blood pressure 'dipping' pattern.



1. Schematic of glucocorticoid receptor-mediated activation, via phosphorylation of the NCC cotransporter in the DCT of the kidney.

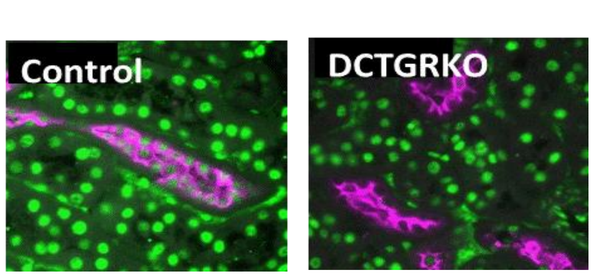
Hypothesis and key questions

"The glucocorticoid receptor in the DCT is involved in blood pressure (BP) rhythm".

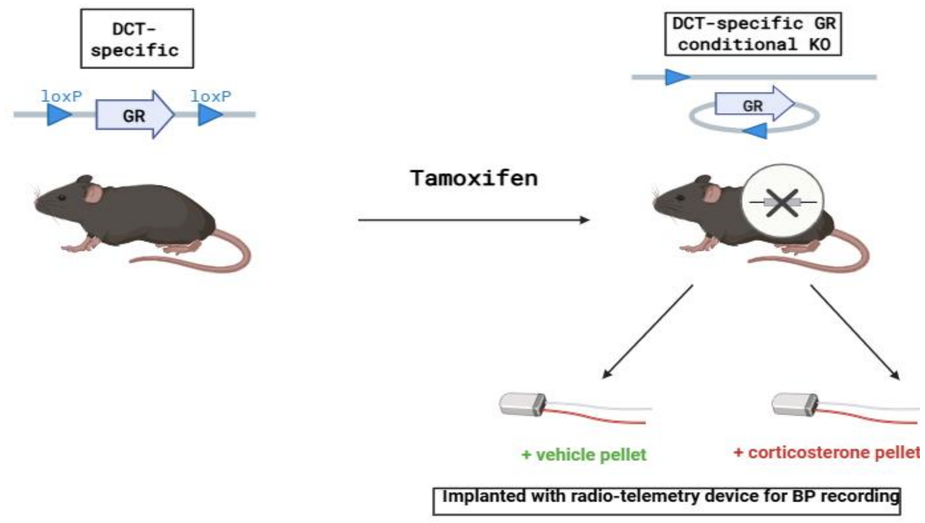
a) Does the GR contribute to baseline BP?
b) Does the GR contribute to glucocorticoid-induced non-dipping BP?

Methods

- **Animals:** Animals: DCTGRKO mice were generated by crossing mice with GR flanked by loxP sites with a tamoxifen-inducible Cre driven by the NCC-promoter to specifically target the DCT. Cre-mediated excision of GR was achieved by administration of tamoxifen for 5 days. Experiments were performed in control littermates (GRfl/fl) and DCTGRKO (DCT Cre+/-. GRfl/fl) mice after a 2 week "washout" period. Confirmed GR knock out in DCTGRKO is shown in Fig2.
- **Radio-telemetry:** Mice were surgically implanted with radio-telemetry devices under isoflurane. After postoperative recovery, blood pressure, heart rate, and activity were recorded in conscious, unrestrained mice for 1 minute every 20 minutes. After a 7-day baseline period, mice received either corticosterone or vehicle pellets.
- **Treatment:** To maintain stable plasma corticosterone levels and eliminate the influence of the natural circadian rhythm, 25 mg corticosterone pellets were subcutaneously implanted under isoflurane anaesthesia. Vehicle pellets were made up of the inert matrix without hormone.



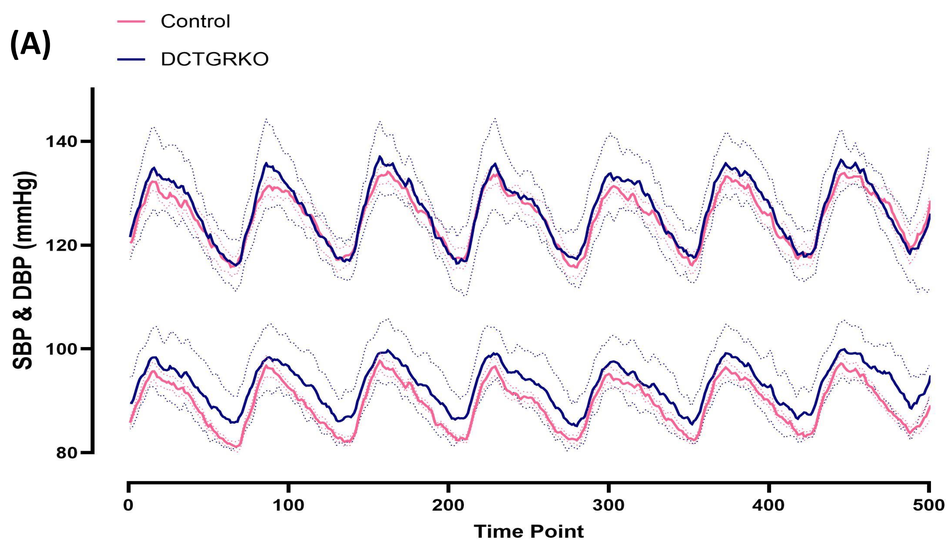
2. In DCTGRKO mice, glucocorticoid receptor (GR; green) was absent from the nuclei of cells in the distal convoluted tubule, identified by NCC expression (magenta). This confirms the DCTGRKO as successful.



3. Schematic of the methodology involved in this project

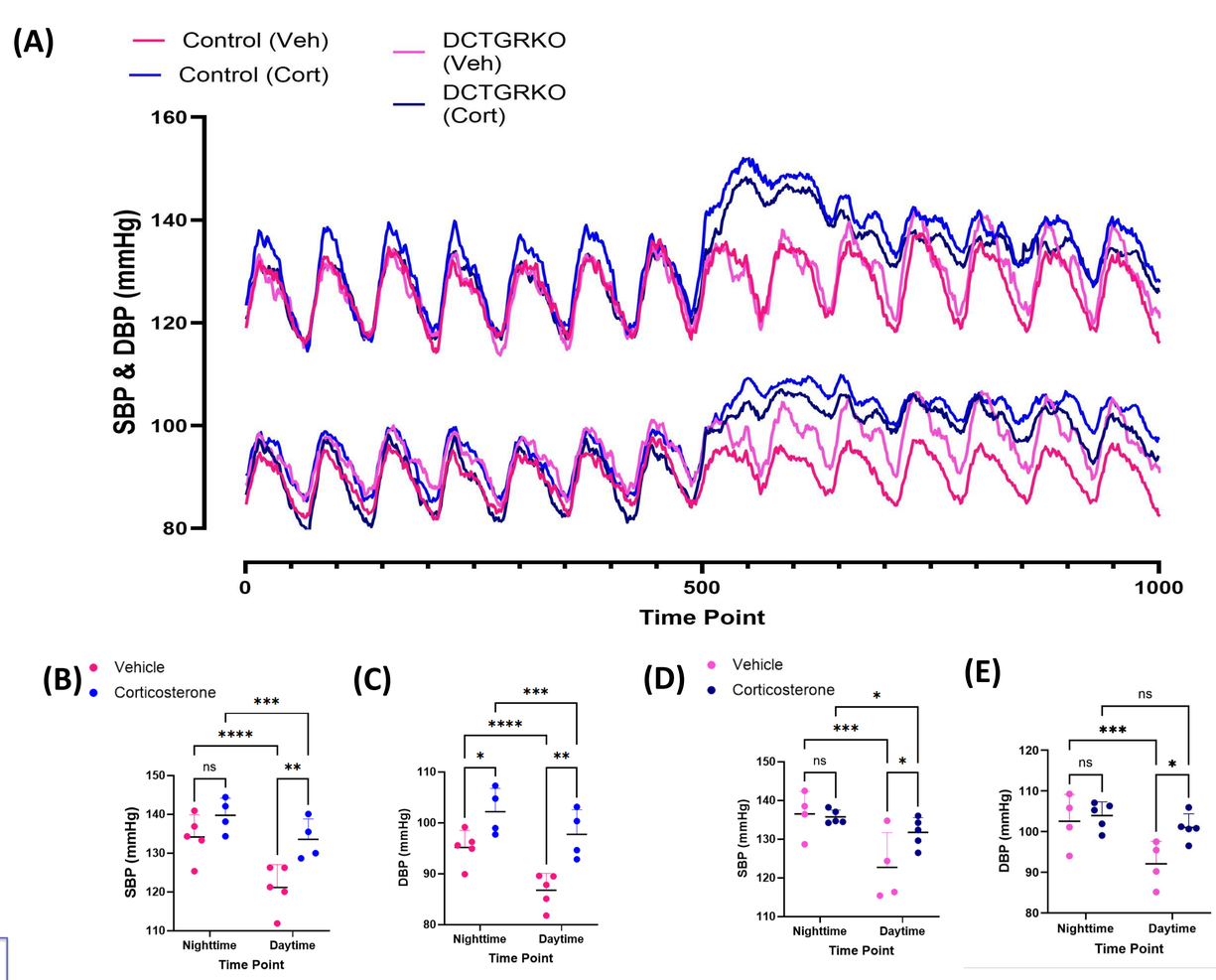
Results

4. GR in the DCT does not contribute to baseline BP



(A) Rolling averages of SBP and DBP in control and DCTGRKO mice at baseline. (B) SBP of control and DCTGRKO mice at night (averaged over 10 nights, 10pm-3am) versus day (averaged over 10 days, 10am-3pm). (C) DBP of control and DCTGRKO mice (averaged over 10 nights, 10pm-3am) versus day (averaged over 10 days, 10am-3pm. Data E-H were analysed by 2-way ANOVA with post hoc Fisher's LSD tests where ****p<0.0001, n=9-10.

5. DCTGRKO does not prevent glucocorticoid-induced non-dipping BP



(A) 5 hourly rolling averages of SBP and DBP in control and DCTGRKO mice with veh/cort treatment (pre-pellet/post-pellet). (B) SBP of control mice at night (averaged over 10 nights, 10pm-3am) versus day (averaged over 10 days, 10am-3pm). (C) DBP of control mice (averaged over 10 nights, 10pm-3am) versus day (averaged over 10 days, 10am-3pm (D) SBP of DCTGRKO (averaged over 10 nights, 10pm-3am) versus day (averaged over 10 days, 10am-3pm) (E) DBP of DCTGRKO (averaged over 10 nights, 10pm-3am) versus day (averaged over 10 days, 10am-3pm). Data are mean only (A) or mean±SD (A-E). Data A-E were analysed by 2-way ANOVA with post hoc Fisher's LSD tests where ***p<0.001, **p<0.01, *p<0.5, n=4-5.

Conclusions

- GR in the DCT does not contribute to baseline blood pressure regulation.
- Glucocorticoid signalling within the DCT of control mice increases SBP and DBP and prevents a dip in BP.
- DCTGRKO does not rescue glucocorticoid-induced elevated BP and non-dipping BP in mice.

Acknowledgements

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References

1. Tang, A., Yang, E. and Ebinger, J.E. (2023) 'Non-Dipping blood pressure or nocturnal hypertension: Does one matter more?,' *Current Hypertension Reports*, 26(1), pp. 21–30.
2. Ivy, J.R. *et al.* (2019) 'Glucocorticoid receptor activation stimulates the sodium-chloride cotransporter and influences the diurnal rhythm of its phosphorylation,' *AJP Renal Physiology*, 317(6), pp. F1536–F1548.