

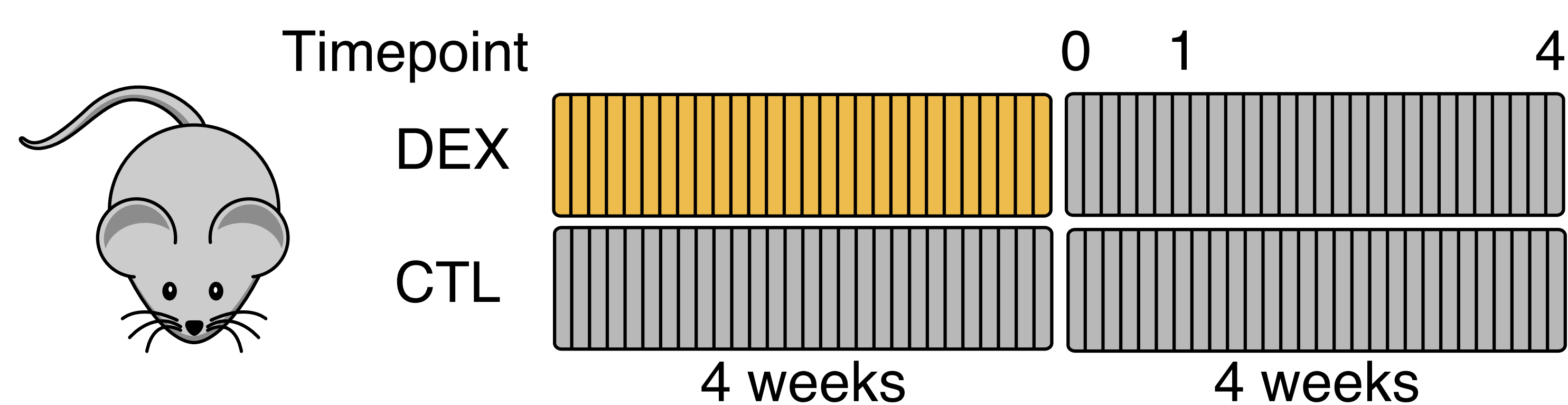
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Introduction

- Glucocorticoids (GC) are prescribed for periods >3 months to 1% of the UK population.
- 10-30% of patients treated with chronic GC develop adrenal insufficiency.
- Understanding the mechanisms resulting in HPA axis failure may allow us to predict those at risk, inform treatment strategies and reduce the potential risks of adrenal insufficiency.
- To explore these mechanisms, we have developed a mouse model of GC-induced HPA axis dysfunction.

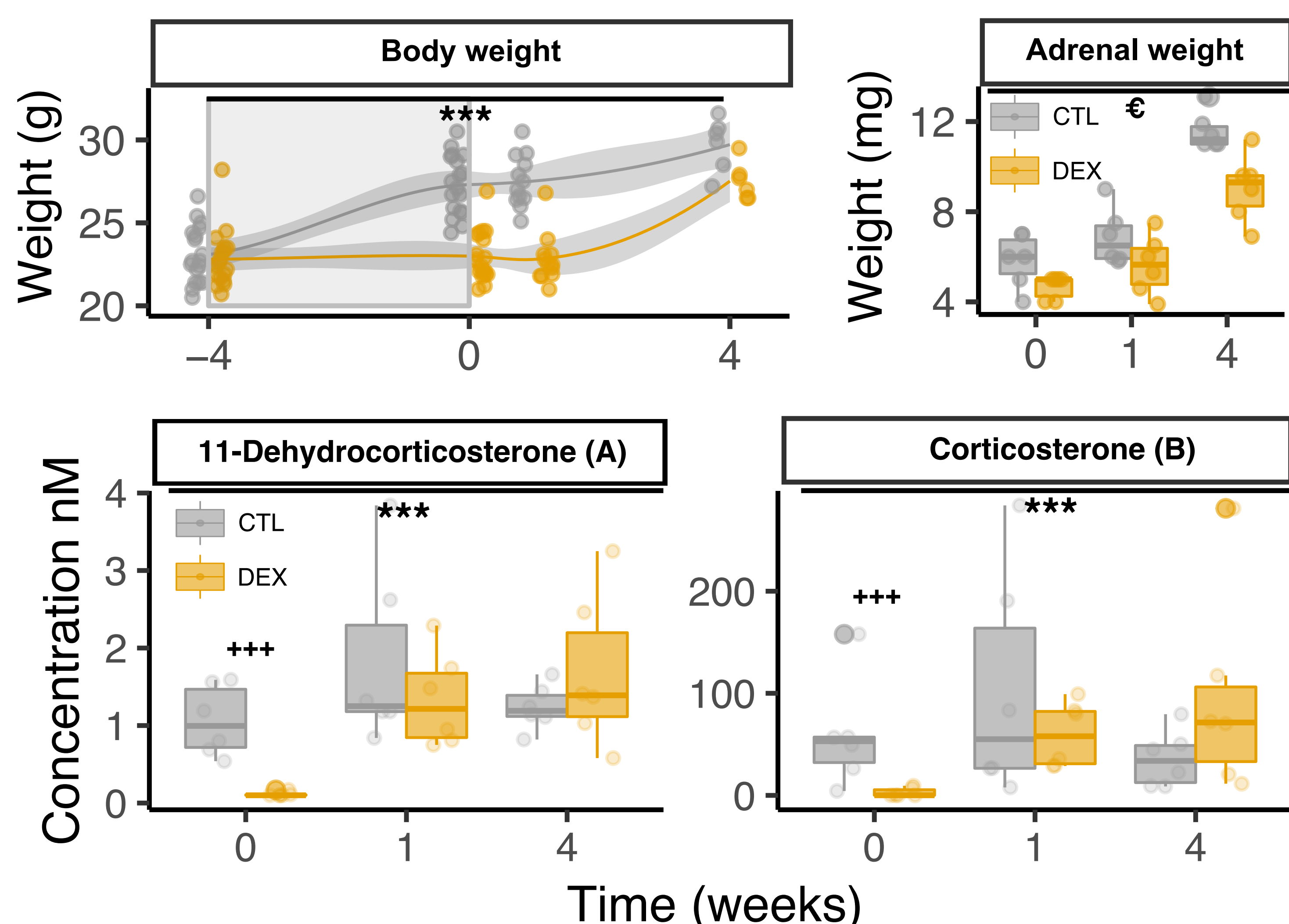
Methods

- 36 C57BL/6 mice were randomly assigned to receive dexamethasone (DEX) (~10ug/day) or vehicle via drinking water for four weeks.
- At 4 weeks (time 0) both groups received only drinking water.
- Tissues were harvested at 0, 1 and 4 weeks following withdrawal of treatment.
- Serum 11-Dehydrocorticosterone(A) and Corticosterone(B) were measured by LCMS/MS.
- Hypothalamus, pituitary and adrenal activity was assessed by qPCR.



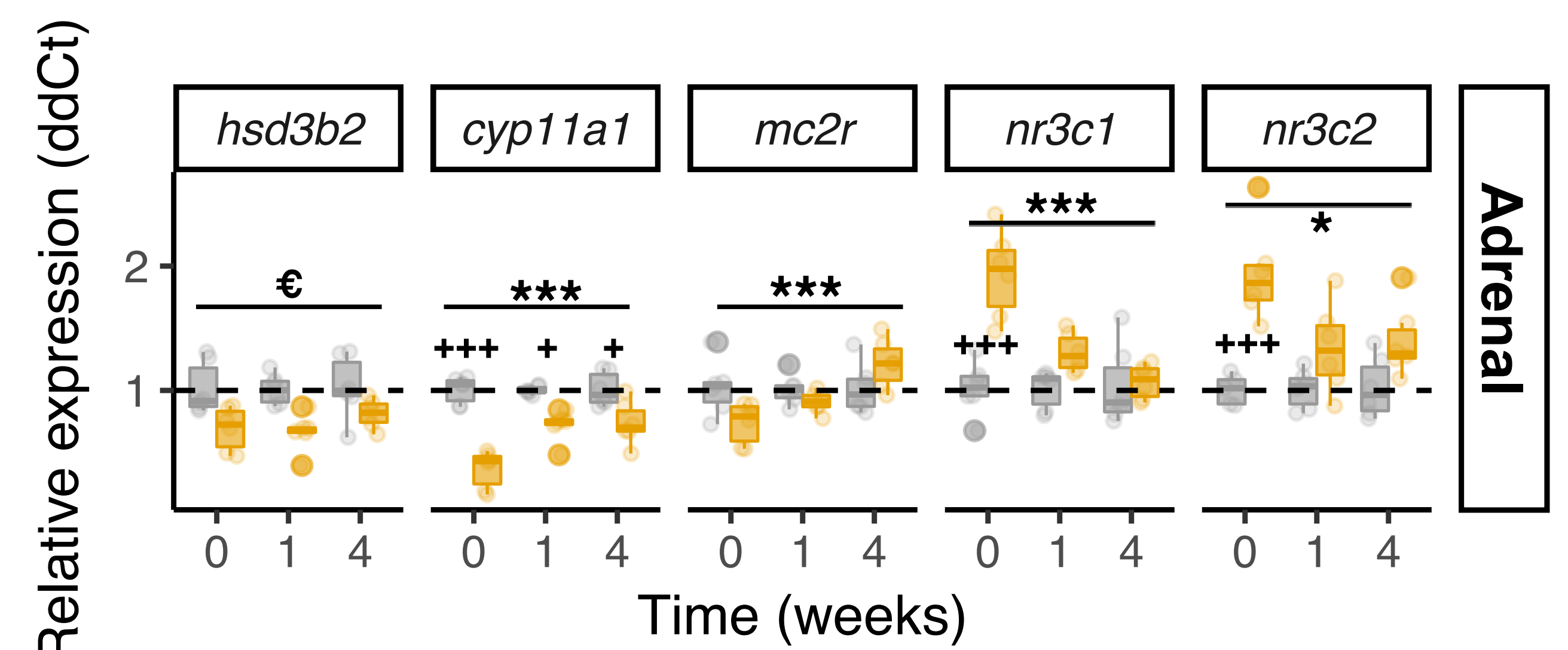
Results

Effects of Dexamethasone on body weight, adrenal weight and steroid production



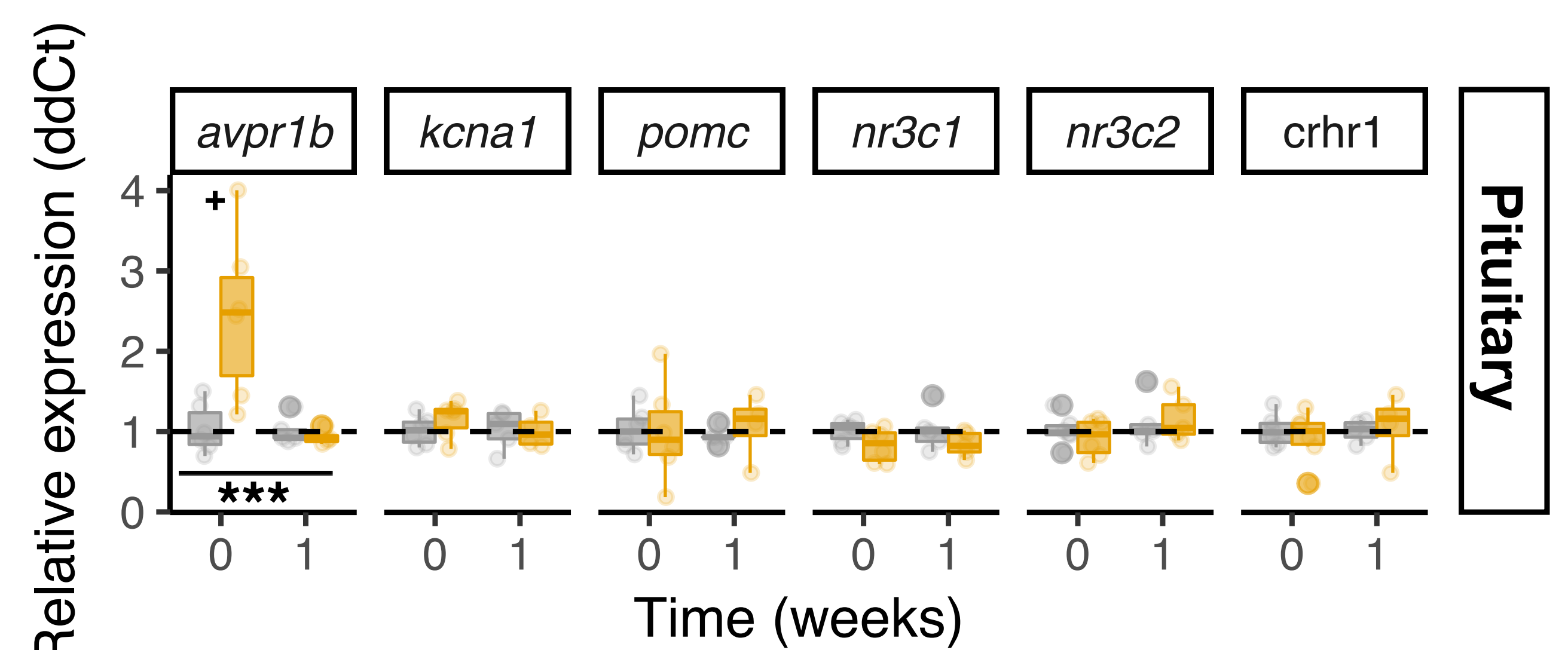
DEX Impairs growth, which recovers by week 4. Results in persistent reduced adrenal weight. Suppresses A and B, which recover by week 1.

Expression of key HPA axis genes



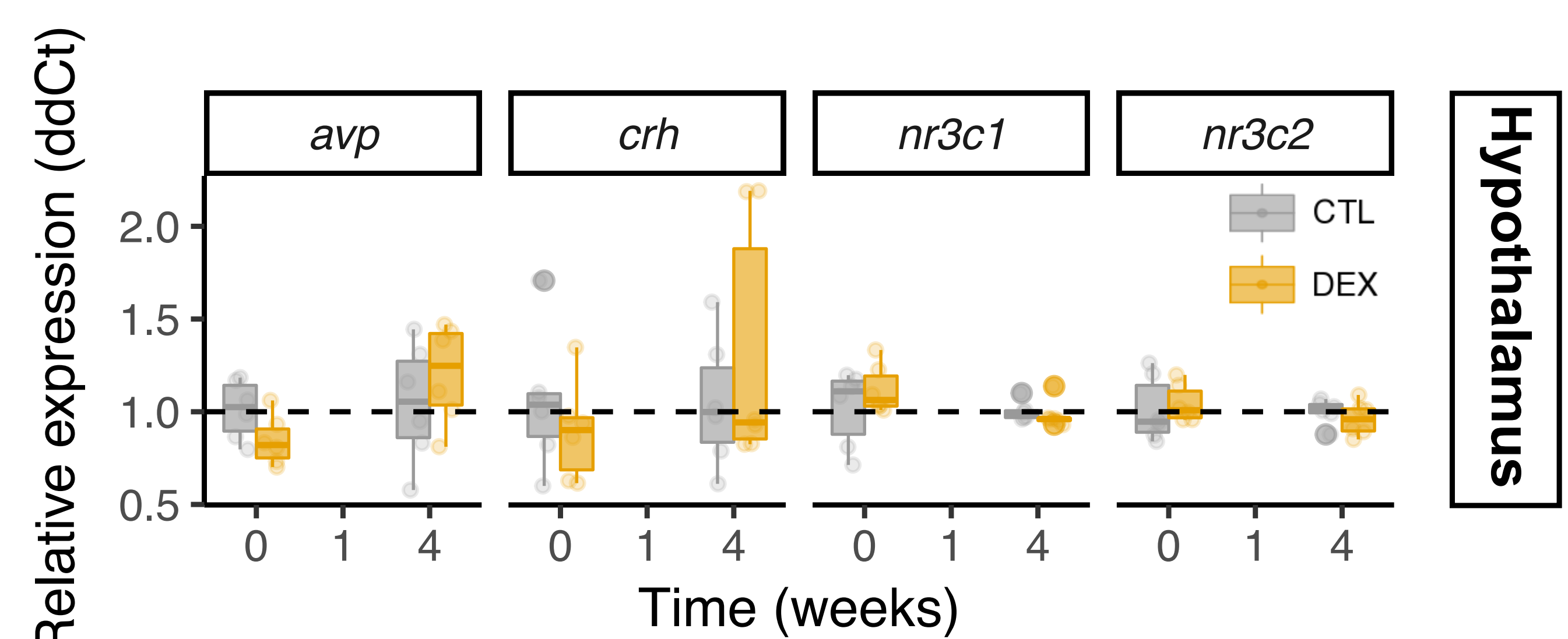
DEX

Reduces expression of enzymes *hsd3b2* and *cyp11a1*. Reduces ACTH receptor expression, compensation by week 4. Increases GR and MR mRNA expression.



DEX

Increases AVP receptor expression. No effect on whole pituitary *pomc* expression (possibly melanotroph effect).



DEX

No significant effect to hypothalamic mRNA expression. Trend for reduced AVP and CRH at time 0.

Data analysed by linear mixed model with timepoint and treatment as fixed factors and cage as a random factor. * significant interaction between treatment and time. € significant effect of fixed effect (treatment) only. + significance determined by Tukey adjusted post hoc testing. xxx $p < 0.001$; xx $p < 0.01$; x $p < 0.05$. n = 6.

Conclusions

- 4 weeks dexamethasone treatment in mice results in suppression of A and B production which has recovered 1 week later.
- At 1 and 4 weeks following treatment withdrawal there is evidence of adrenal compensation of higher axis dysfunction (reduced adrenal size, increased *mc2r* expression).
- Examining the first week of recovery may inform mechanisms Glucocorticoid production recovered more quickly in this model compared to human treatments.