The hypothalamic-pituitary-adrenal axis is hyperactive in humans and rodents that are heterozygous for null mutations of the glucocorticoid receptor (GR+) (1).

GR+/- mice have increased renal mass and salt-sensitive hypertension perhaps due to excess mineralocorticoid activity (2).

Renal mechanisms of hypertension have been investigated but the adrenal phenotype of GR+/- mice has yet to be studied.

Results

![Figure 1: GR deficiency differentially affects cortical and medulla cell size.](image1.png)

In H & E stained sections, the cross-sectional area (mean ± SE, n=5-6) of outer zona fasciculata cells (ZF) was increased in HET adrenals (p<0.05) but medullary cells were smaller (p>0.05). ZG and inner ZF cells were not significantly affected. Adrenal mass was increased in HET mice, but this was not statistically significant in this cohort (data not shown).

![Figure 2: GR deficiency reduces cell proliferation in the adrenal cortex.](image2.png)

Numbers of BrdU positive nuclei were reduced (p<0.01) in the cortex of HET mice, but were not significantly affected in the medulla.

![Figure 3: GR deficiency affects BrdU cell distribution.](image3.png)

Cumulative distribution curves show distances from capsule of BrdU-positive cells in sections of WT and HET adrenals as they migrate inwards towards the medulla. There is a significant inward shift (p<0.001) in HET sections. However, this could reflect proportionately fewer proliferating cells in outermost ZG regions of HET adrenals.

![Figure 4: GR deficiency does not affect apoptosis.](image4.png)

TUNEL staining (blue, arrows) was variable in WT (A) and HET (B). There were no significant qualitative or quantitative differences between WT & HET mice.

![Figure 5: BrdU+ve cells express 11β-OH but not AS.](image5.png)

BrdU (green nuclei) and 11β-OH (red) often co-localise in ZF cells but AS+ve ZG cells (red) are BrdU-negative. This pattern was seen in both HET and WT adrenals with perhaps greater 11β-OH intensity in HETs.

Conclusions

Impaired negative feedback of the hypothalamic-pituitary-adrenal axis in GR+/- mice may cause ACTH-dependent hypertrophy but not hyperplasia of the glucocorticoid-synthesising ZF cells.

Urinary aldosterone is increased in GR+/- mice but this does not appear to be due to ZG cell hypertrophy or hyperplasia. Steroid-dependent hypertension may explain the counter-regulatory decrease in medulla cell size.

References:

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