11ß-HYDROXYSTEROID DEHYDROGENASE TYPE 2 (11ß-HSD2) KNOCKOUT MICE AS MODEL OF PRENATAL GLUCOCORTICOID PROGRAMMING

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11ß-Hydroxysteroid dehydrogenase type 2 (11ß-HSD2) inactivates glucocorticoids by conversion of corticosterone to 11-dehydrocorticosterone in rats and mice. 11ß-HSD2 is highly expressed in both the placenta and developing regions of the fetal and neonatal brain. The enzyme is thus believed to provide a barrier to maternal glucocorticoids and protect the developing fetus from exposure to excessive levels during a period in which they could have detrimental effects (Meyer, 1983).

The aim of this study was to determine whether loss of 11ß-HSD2 results in lifelong programming of anxiety-related behaviour, hypothalamic-pituitary-adrenal (HPA) axis and central gene expression.

11ß-HSD2 knockout (11ß-HSD2ko) and wild-type C57BL/6 (WT) mice were weighed at birth. Behavioural analysis was performed using the elevated plus maze (EPM) and open field apparatus (OF) whilst plasma corticosterone levels were measured by RIA under basal and post restraint conditions. Expression levels of the glucocorticoid (GR) and mineralocorticoid receptors (MR), in addition to corticosteroid releasing factor (CRF) were assessed by in situ hybridization histochemistry within the paraventricular nucleus (PVN) of the hypothalamus, hippocampus and amygdala. Results are expressed as mean±SEM and were compared using the Student's unpaired t-test or two-way analysis of variance with Bonferroni's post-hoc test, where appropriate.

11ß-HSD2ko displayed decreased birth weight (1.14±0.02g vs 1.33±0.02g; n=26-27; $P<0.001$) compared to WT. In behavioural tests, 11ß-HSD2ko entered the open arms of the EPM more (32.1±3.5% vs 18.8±3.0%; n=26-27; $P<0.01$)) and spent longer on them (35.7±4.6% vs 19.9±4.9%; n=26-27; $P<0.05$) compared to WT. In addition, they made a greater proportion of crossings within the more anxiogenic inner zone of the OF than WT mice (31.3±1.5% vs 23.8±2.4%; n=26-27; $P<0.05$). However, 11ß-HSD2ko did not differ from WT in either basal or post restraint plasma corticosterone levels, although adrenal weights were decreased (1.24±0.07g vs 2.02±0.15g; n=10; $P<0.001$). Some differences were noted in gene expression between 11ß-HSD2ko and WT. Postnatal day 21 (P21) 11ß-HSD2ko displayed lower but not significant expression of CRF mRNA within the PVN (170.1±32.7 vs 384.9±100.4 grains/neuron; n=3-6; $P=0.19$), whilst expression in the central amygdala was unaltered. GR expression was unchanged in adult hippocampal subregions, whilst being significantly decreased throughout the hippocampus of the P21 11ß-HSD2ko (48.0±10.8 vs 84.1±9.4 grains/neuron; n=5-6; $P<0.05$), particularly within the CA1 subregion (69.7±8.1 vs 138.7±46.2 grains/neuron; n=5-6; $P<0.05$). Hippocampal MR expression did not differ between 11ß-HSD2ko and WT in either P21 or adult mice.

Our data show that loss of 11ß-HSD2 results in lower birth weight and an anxious phenotype. These mice also display a dysregulated HPA axis and altered central GR mRNA expression within the hippocampus although only in young (P21), and not adult mice. Findings are similar to those previously investigated within prenatal glucocorticoid programming (Welberg et al., 2000; Welberg et al., 2001) in the rat, suggesting that 11ß-HSD2ko mice are a good model of glucocorticoid programming.

Meyer, J.S. (1983) *Exp Neurol* **82**, 432-446.
Welberg, L.A. *et al*. (2000) *Eur J Neurosci* **12**, 1047-1054.
Welberg, L.A. *et al*. (2001) *Neuroscience* **104**, 71-79.

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