CORTISOL DECREASES HIPPOCAMPAL NEUROGENESIS BY REGULATING THE ENZYME SGK1

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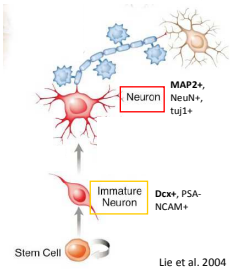
BACKGROUND

• Glucocorticoids and adult hippocampal neurogenesis in depression

- Increased levels of glucocorticoid hormones are commonly observed in situations of chronic stress and in depression.
- High levels of glucocorticoid hormones decrease adult hippocampal neurogenesis
- Adult hippocampal neurogenesis has recently been demonstrated to contribute to the development of depressive symptoms in situations of stress (Snyder et al., 2011)
- Glucocorticoids (cortisol in humans) can activate two intracellular receptors:
  - → Mineralocorticoid Receptor (MR), high affinity
  - → Glucocorticoid Receptor (GR), low affinity



- The enzyme, serum- and glucocorticoid-regulated kinase 1 (SGK1) mediates some effects of glucocorticoids on working memory, oligodendrocyte morphology and glucocorticoid responsiveness. (Yuen et al., 2011; Miyata et al., 2011, Luca et al., 2009)
- GR function is critically regulated by phosphorylation at the serine residues S203, S211 and S226.

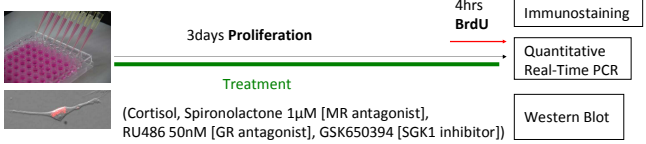
HYPOTHESIS

- MR activation mediates the effects of low cortisol concentrations, while high concentrations of cortisol activate the GR in human hippocampal progenitor cells.
- Cortisol decreases human hippocampal neurogenesis via GR-dependent upregulation of SGK1.
- SGK1 regulates GR function by phosphorylation.

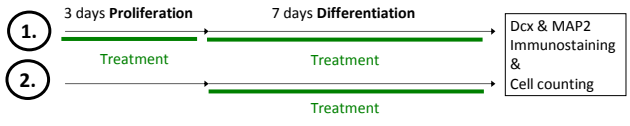
METHODS

- Human embryonic hippocampal progenitor cell line HPC03A/07 (ReNeuron, UK)

• Proliferation assay

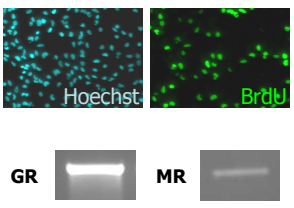


• Differentiation assay



RESULTS

• Bimodal effects of cortisol on cell proliferation



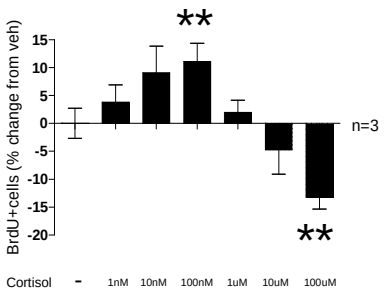


Figure 1. Low concentrations of cortisol (100nM) increase proliferation, while high concentrations (100µM) decrease proliferation.**p<0.01

• MR- and GR-dependent effects of cortisol on proliferation

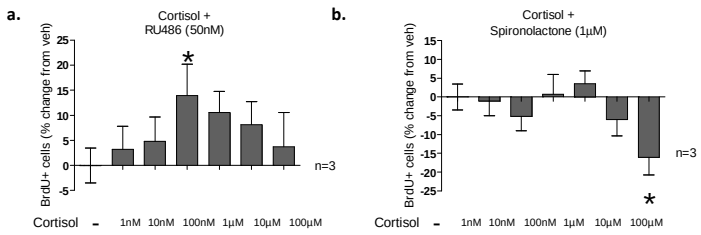


Figure 2. (a) The MR-antagonist, spironolactone, blocks the increase in proliferation. **(b)** The GR-antagonist, RU486, blocks the decrease in proliferation. *p<0.05

• Cortisol decreases neuronal differentiation

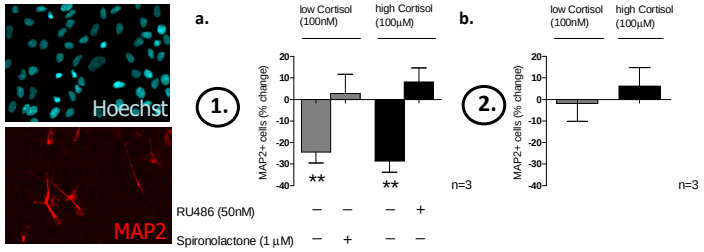


Figure 3. (a) Cortisol treatment during proliferation and differentiation (paradigm ①) decreases neuronal differentiation at both 100nM and 100µM via MR and GR-dependent effects, respectively. **(b)** Treatment only during the differentiation phase (paradigm ②) has no effect. **p<0.01

• GR activation by cortisol increases SGK1 expression

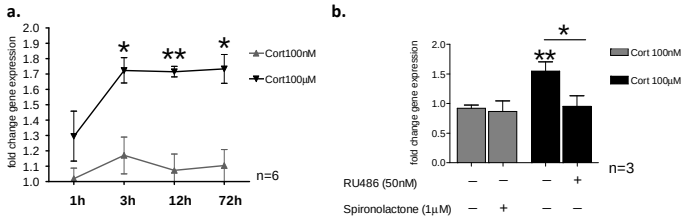


Figure 4. (a) High cortisol concentrations increase SGK1 expression. **(b)** The effect at 12hrs is blocked by RU486 (50nM). *p<0.05, **p<0.01

• SGK1 mediates the cortisol-induced reduction in neurogenesis

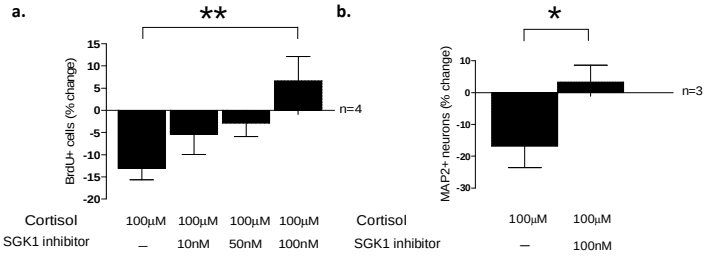


Figure 5. The SGK1-inhibitor, GSK650394, counteracts the effects of cortisol (100µM) on **(a)** proliferation and **(b)** neuronal differentiation.*p<0.05, **p<0.01

• SGK1 phosphorylates the GR

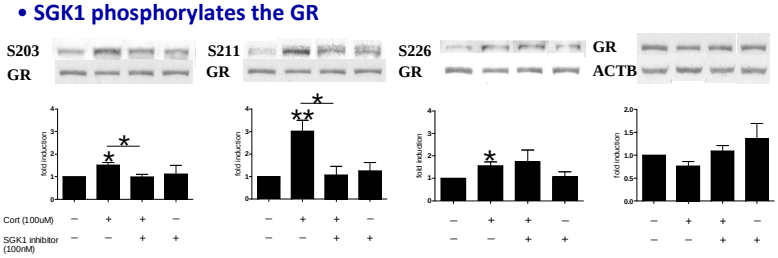


Figure 6. The SGK1-inhibitor, GSK650394, counteracts the cortisol-induced GR phosphorylation at S203 and S211, but not at S226. *p<0.05, **p<0.01

CONCLUSIONS

- MR activation by low concentrations of cortisol increases proliferation, while GR activation by high concentrations decreases proliferation
- GR-dependent activation of SGK1 expression mediates the cortisol-induced reduction in neurogenesis
- Cortisol-induced SGK1 expression activates the GR by phosphorylation at the GR serine residues S203 and S211

DISCLOSURE: This poster is financially supported by the European Union Framework7, the Medical Research Council UK and an NIHR BRC studentship in Biomedical and Mental Health to C. Anacker. J. Price acts as a consultant for ReNeuron, UK.