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, but not at S226. *p<0.05, **p<0.01

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

- 3 days Proliferation
- 4 days BrdU

- Treatment
  - Cortisol, Spironolactone 100nM (MR antagonist), RU486 50nM (GR antagonist), GSK650394 (SGK1 inhibitor)

Differentiation assay

- 3 days Proliferation
- 7 days Differentiation
- Treatment
  - Dcx & MAP2

RESULTS

- Bimodal effects of cortisol on cell proliferation

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