Antidepressants modulate human hippocampal neurogenesis by activating the glucocorticoid receptor

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ABSTRACT
Antidepressants increase adult hippocampal neurogenesis and promote neuronal differentiation in rodents, but the underlying molecular mechanisms are unknown. Here we treated human embryonic hippocampal progenitor cells with the antidepressant, sertraline, and investigated changes in cell proliferation and neuronal differentiation. We find that antidepressants increase neuronal differentiation and decrease cell proliferation by activating the glucocorticoid receptor (GR), and by increasing GR-mediated gene transcription of the cell cycle inhibitors p27Kip1 and p57Kip2.

BACKGROUND

• Adult neurogenesis & Depression
  - Chronic stress and depression are associated with elevated levels of glucocorticoid hormones and with decreased hippocampal neurogenesis. (Gould et al., 1992; David et al., 2009; Boldrini et al., 2009).

• Antidepressants increase adult hippocampal neurogenesis, and thereby possibly contribute to the resolution of some of the behavioural deficits in depression (Santarelli et al., 2003; David et al., 2009).

• Antidepressants enhance neuronal differentiation of hippocampal progenitor cells (Wang et al., 2008).

• Antidepressants increase progenitor cell proliferation in depressed patients or in mice which are co-treated with glucocorticoids (Boldrini et al., 2009; David et al., 2009).

Glucocorticoids and antidepressants both activate the glucocorticoid receptor (GR). The GR is a nuclear transcription factor, and GR–transactivation (GR binding to DNA) induces transcription of the cyclin-dependent kinase 2 (CDK2)-inhibitors p27Kip1 and p57Kip2, which have been implicated in early neuronal development (Pariante et al., 1997; Shin et al., 2009; Ye et al., 2009).

HYPOTHESIS

• Antidepressants enhance neuronal differentiation, but increase progenitor cell proliferation only in the presence of glucocorticoids

• The effect of antidepressants on neurogenesis is dependent on the glucocorticoid receptor (GR)

• GR-dependent expression of the CDK2-inhibitors p27Kip1 and p57Kip2 mediates the effect of antidepressants on proliferation and neuronal differentiation

METHODS

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

• Proliferation assay

- 3days Proliferation
- 4hrs BrdU immunostaining
- BrdU binding assay

• Differentiation assay

- 3 days Proliferation
- 7 days Differentiation

- Dcx & MAP2 Immunostaining
- Cell counting

RESULTS

• Antidepressants modulate hippocampal progenitor cell proliferation by activating the GR

• Antidepressants induce GR transactivation and decrease GR expression

• Antidepressants induce expression of p27Kip1 and p57Kip2

• Antidepressants enhance neuronal differentiation and promote neuronal maturation by activating the GR

CONCLUSIONS

• Sertraline decreases progenitor cell proliferation via a GR-dependent effect; cell proliferation is only increased in the presence of glucocorticoids (Fig 1)

• Sertraline induces GR transactivation, decreases GR expression, and increases the CDK2-inhibitors p27Kip1 and p57Kip2 during cell proliferation (Fig 2)

• Sertraline increases neuronal differentiation and maturation via a GR-dependent effect, but only if already present during the proliferation phase (Fig 3)