Antidepressants modulate human hippocampal neurogenesis by activating the glucocorticoid receptor

Christoph Anacker, Patricia A. Zunszain, Annamaria Cattaneo, Livia A. Carvalho, Sandrine Thuret, Jack Price, Carmine M. Pariante

Centre for the Cellular Basis of Behaviour, Institute of Psychiatry, King's College London, United Kingdom

email.: Christoph.Anacker@kcl.ac.uk

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 $p27^{Kip1}$ and $p57^{Kip2}$.

BACKGROUND

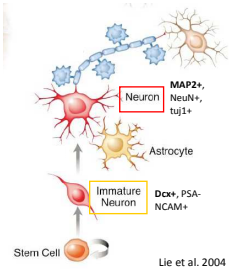
• Adult neurogenesis & Depression

▪ 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).



Lie et al. 2004

▪ 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 $p27^{Kip1}$ and $p57^{Kip2}$, 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

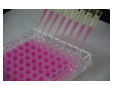
▪ The effect of antidepressants on neurogenesis is dependent on the glucocorticoid receptor (GR)

▪ GR-dependent expression of the CDK2-inhibtiors $p27^{Kip1}$ and $p57^{Kip2}$ 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**

Treatment

(DEX, antidepressants, DEX & antidepressants)

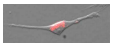
BrdU Immunostaining

GR-DNA binding assay

Quantitative Real-time PCR

Western Blot

• Differentiation assay



3 days **Proliferation**

7 days **Differentiation**

1. Treatment
2. Treatment — Treatment
3. Treatment

Dcx & MAP2 Immunostaining & Cell counting

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

J. Price acts as a consultant for ReNeuron Group

RESULTS

• Antidepressants modulate hippocampal progenitor cell proliferation by activating the GR

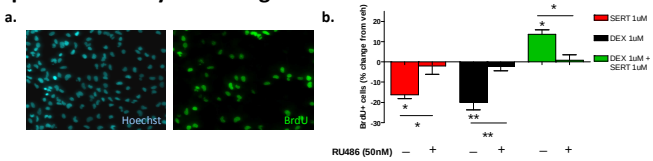


Figure 1. BrdU immunocytochemistry **(a)**. Sertraline (SERT 1uM, red bars) and the glucocorticoid dexamethasone (DEX 1uM, black bars) decrease cell proliferation. Only DEX and SERT co-treatment increases cell proliferation (green bars). These effects are abolished by the GR-antagonist RU486 (50nM) **(b)**. *p<0.05, **p<0.01, n=5

• Antidepressants induce GR transactivation and decrease GR expression

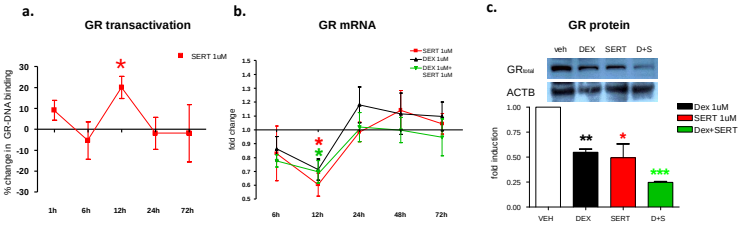
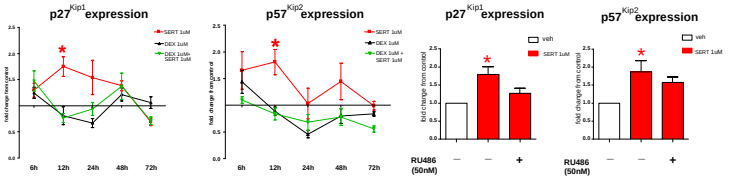


Figure 2. Sertraline induces GR-transactivation **(a)** and decreases GR mRNA **(b)** and protein **(c)** after 12h of cell proliferation. *p<0.05, **p<0.01, ***p0.001; n=3

• Antidepressants induce expression of $p27^{Kip1}$ and $p57^{Kip2}$



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

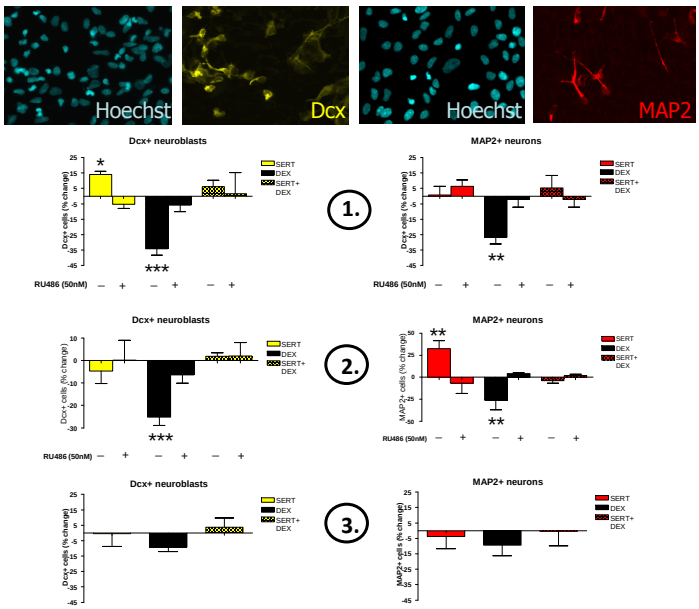


Figure 3. Sertraline induces differentiation into Dcx+ cells **(1)** and promotes neuronal maturation into MAP2+ cells **(2)**. This effect is absent if sertraline is not present during the proliferation phase **(3)**. *p<0.05, **p<0.01, ***p0.001; n=5

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 $p27^{Kip1}$ and $p57^{Kip2}$ 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**)