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COMMENTARY

Differentiation of hippocampal stem cells into functional neurons: evolving our understanding of monoamine oxidase-A inhibition

*,[1]Colin G. Egan

[1]Department of Neuroscience, Center for Stem Cells, Molecular Medicine Section, Azienda Ospedaliera, University of Siena, U. O. Medicina Molecolare, Policlinico 'Le Scotte' viale Bracci, Siena 53100, Italy

Depression affects many millions of people worldwide and much is still unknown with respect to the mode of action of antidepressant drugs. The hippocampus has been associated with many psychiatric disorders, including clinical depression. Recently, stem cells have also been shown to reside within discrete regions of the hippocampus and can differentiate under a variety of conditions into neural cells. In this issue, Chiou *et al*. have elegantly demonstrated that cells isolated from the rat hippocampus, and treated with the antidepressant moclobemide, may be differentiated *in vitro* into neural cells exhibiting features to those of serotoninergic neurons. They have also suggested that this process was mediated, in part, through the expression of specific antiapoptotic genes (Bcl-2 and Bcl-XL) and *via* activation of extracellular-regulated kinase. This work raises the attractive possibility that the use of antidepressants, such as moclobemide, may exert neuroprotective and potentially neurogenerative effects not just *in vitro*, but also *in vivo*, through the selected differentiation of stem cells into functional neurons. The exact mechanisms by which such antidepressants differentiate neural stem cells still remains to be fully elucidated.
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Abbreviations: CREB, cAMP response element binding protein; ERK, extracellular regulated kinase; 5-HT, 5-hydroxytryptamine; MAO, monoamine oxidase-A; MAPK, mitogen-activated protein kinase; MB, moclobemide; NSCs, neural stem cells

Neurological and psychiatric disorders such as Parkinson's disease, Alzheimer disease and depression may be treated with drugs to alleviate pain and symptoms; however, no current therapy is available yet which may actually repair or replace damaged tissues. The mammalian hippocampus is recognized to be at least one region of the brain that possesses the capability to form new neurons during adult life. This process of neurogenesis occurs in the subgranular zone within the dentate gyrus (Taupin & Gage, 2002). The rat hippocampus is richly innervated with serotoninergic fibers (5-HT), and the observation that antidepressant drugs (such as moclobemide) promote neurogenesis has led to the thinking that the serotoninergic neurotransmitter system plays an important role in the initiation of neurogenesis in the hippocampus. Therefore, with this in mind, Chiou *et al*. (2006) examined the effect of the antidepressant moclobemide (MB), upon neural stem cells isolated from the rat hippocampus, and its role in neurogenesis, neuroprotection and neural differentiation.

MB is an antidepressant drug, which affects the monoaminergic cerebral neurotransmitter system through the reversal inhibition of monoamine oxidase (MAO), preferentially type A. This decreases the metabolism of the neurotransmitters noradrenaline, dopamine and 5-HT and increases their extracellular concentrations. Chiou *et al*. have used MB at a dose which is within the IC_{50} range and similar to that which has been previously used to inhibit MAO in cultured cells (Li *et al*., 2004). In order to examine the viability of NSCs in the presence of MB, they cultured cells with the addition of 50 and 200 μM MB compared to control. A biphasic effect was observed, where at the high dose (200 μM), cells did not survive, whereas at 50 μM, cell viability was in fact increased over that of control levels. Interestingly, within the clinic, MB does not precipitate 5-HT toxicity in overdose by itself, nor does it produce serotoninergic side effects (Isbister *et al*., 2003). It is likely that MB upregulates other neurotransmitter systems in addition to that of the serotoninergic, especially at high doses, which may also contribute to cell toxicity. In fact, Chiou *et al*. detected other neurotransmitters in addition to 5-HT, including dopamine by HPLC analysis, supporting this idea.

More interesting perhaps, by Chiou *et al*., was the finding that treatment of cells with MB at the lower concentration of 50 μM increased cell survival, pointing towards the possibility that MB may be in fact exerting neurogenic effects. In addition, these findings corroborate with a report by Li *et al*. (2004), who have shown that MB upregulated proliferation of hippocampal progenitor cells in chronically stressed mice. Furthermore, Chiou *et al*. have demonstrated that NSCs cultured in the presence of MB also increased the expression of the antiapoptotic genes, Bcl-2 and Bcl-X_L, in a time-dependent manner. In fact, transplantation of embryonic stem cells overexpressing Bcl-2 has been previously reported to promote functional recovery of cerebral ischemia in the rat (Wei *et al*., 2005). Thus, the role of Bcl-2 in neurogenesis exists in both

*Author for correspondence; E-mail: egan@unisi.it

embryonic and adult life and does not appear to be restricted to developmental changes.

The signaling mechanisms underlying Bcl-2 expression are not completely understood. However, it is known that activation of the mitogen-activated protein kinase pathway (MAPK) increases Bcl-2 expression (Tao *et al*., 1998). Consistent with these findings, Chiou *et al*. (2006) reported that MB increased Bcl-2 in NSCs in an MAPK-dependent manner, as they prevented the expression of Bcl-2 and activation of ERK1/2 with PD98059. Moreover, Chiou *et al*. further demonstrate that neurite development of MB-treated differentiated NSCs was upregulated by the phosphorylation of ERK1/2. This pathway may also involve the transcription factor CREB (cAMP response element binding protein) as reported by Riccio *et al*. (1999). Interestingly, in other non-neural tissue types, such as vascular smooth muscle, there is differential regulation of CREB (Egan & Nixon, 2004), in proliferative and differentiative phenotypes, thus highlighting the potential importance of this transcription factor in the regulation of NSC to a differentiated functional neuron.

In addition to specific kinases and transcription factors, a myriad of growth factors have been documented to regulate the migration of sensory neuron progenitors in addition to stimulating neurogenesis. One such growth factor, stromal derived growth factor-alpha, and its chemokine receptor CXCR4 have been increasingly recognized for their importance in the mobilization of early precursor cells from the bone marrow into the peripheral blood during ischemia (Wojakowski *et al*., 2004). Recently, CXCR4 has been reported to be elevated on human neural precursors and has also been shown to regulate the migration of neuron progenitors (Belmadani *et al*., 2005). This is one example of many where there are clearly strong similarities between the regulation of hematopoietic and neural stem cells.

In this issue, Chiou *et al*. have made an important contribution in the understanding of the underlying mechanisms by which neurotransmitter systems such as 5-HT may play a role in the process of neurogenesis. The *in vitro* model of NSC culture, which they report is indeed a useful tool to examine novel mechanisms of antidepressant drugs. The exact mechanisms of action of antidepressant drugs such as MB are indeed complex, and whether they initiate mobiliziation and/or differentiation of neural progenitor cells into local or distal regions of hippocampal tissues remains to be established.

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