Adult neurogenesis, cell cycle and drug discovery in psychiatry

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For many years the production of new neurons in mammalian brain was thought to be restricted to development. It is now clear that neurogenesis does occur in adult mammals, including humans (Eriksson *et al*, 1998). Antidepressant drugs and procedures that reduce depression, such as electroconvulsive shock and exercise, increase neurogenesis. The relationships among adult neurogenesis, antidepressant drugs, and depression have generated considerable interest and controversy (Duman, 2004; Scharfman and Hen, 2007).

p21Cip1, a cyclin-dependent kinase inhibitor, restrains cell-cycle progression and proliferation. It is found in neuroblasts and newly developing neurons in the subgranular zone of the hippocampus (Pechnick *et al*, 2008). Chronic treatment with the tricyclic antidepressant imipramine decreases p21Cip1 transcript and protein levels and stimulates neurogenesis in this region. Moreover, mice lacking p21Cip1 have increased rates of hippocampal neurogenesis. Thus, p21Cip1 restrains neurogenesis in the hippocampus, and antidepressant-induced stimulation of neurogenesis might be due to decreased p21Cip1 expression. Cell-cycle regulation occurs downstream from the primary site of action of antidepressants, suggesting that new therapeutic strategies might directly target cell-cycle proteins.

Currently, neurogenesis is a phenomenon in search of a function. There are four key questions that must be answered prior to the implementation of effective treatment strategies directed at altering neurogenesis. First, what is the role of adult neurogenesis in normal brain function? In humans, neurogenesis occurs in the hippocampus and olfactory bulb (Gould, 2007). Advances in imaging technology would help establish the conditions and pathological states under which neurogenesis is altered and whether neurogenesis is a latent process in other brain regions. This information is important because drug-induced stimulation of neurogenesis could disrupt fundamental neurobiological processes. Second, are changes in behavior and/or functional deficits in any disease state due to decreased (or increased) neurogenesis? Excessive neurogenesis could result in inappropriate integration into existing neural networks and could underlie pathological conditions such as epilepsy (Scharfman and Hen, 2007). Drug-induced stimulation of neurogenesis might have unforeseen adverse consequences.

Third, are basal and drug-induced neurogenesis age-dependent in humans? In rodents, the rate of neurogenesis decreases from adolescence to adulthood, and the decline is very steep (Abrous *et al*, 2008). If the rate of neurogenesis is profoundly decreased in older humans, then drugs targeted at stimulating neurogenesis might have limited efficacy in that population. Fourth, are there adverse consequences associated with long-term stimulation of neurogenesis? Long-term and unrelenting stimulation of mitosis without appropriate differentiation and migration could lead to unexpected problems. In addition, it is possible that adult neural stem cells have finite proliferation potentials. Long-term stimulation of neurogenesis might eventually produce premature exhaustion of neuronal precursors, the subsequent loss of therapeutic efficacy and premature 'aging' in the system.

There is a growing list of drugs and behavioral procedures that can stimulate or decrease neurogenesis. Modulating neurogenesis could be a new therapeutic target for the treatment of psychiatric disorders; however, more fundamental information on neurogenesis in humans needs to be obtained to design rational therapeutic strategies and avoid unforeseen adverse consequences.

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Targeting nicotinic receptor antagonists as novel pharmacotherapies for tobacco dependence and relapse

Tobacco dependence is a significant health concern and the most preven-