Neurogenesis and The Effect of Antidepressants

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Abstract: The recent evidence that neurogenesis occurs throughout adulthood and neural stem cells (NSCs) reside in the adult central nervous system (CNS) suggests that the CNS has the potential for self-repair. Beside this potential, the function of newly generated neuronal cells in the adult brain remains the focus of intense research. The hippocampus of patients with depression show signs of atrophy and neuronal loss. This suggests that adult neurogenesis may contribute to the biology of depression. The observations that antidepressants, like fluoxetine, increase neurogenesis in the dentate gyrus (DG) and neurogenesis is required for the behavioral effect of antidepressants, lead to a new theory for depression and the design of new strategies and drugs for the treatment of depression. However, the role of adult neurogenesis in the etiology of depression remains the source of controversies and debates.

Keywords: neural stem cells, hippocampus, depression, fluoxetine, cellular therapy.

Introduction

Neurogenesis, the generation of new neuronal cells, occurs in the adult brain of mammals (Gage, 2000; Gross, 2000), including human (Eriksson et al. 1998). Neurogenesis occurs primarily in two regions of the adult brain: the DG and the subventricular zone (SVZ) (Taupin and Gage, 2001). Newly generated neuronal cells establish synaptic and functional connections with nerve cells of the pre-existing network (Stanfield and Trice, 1988; Markakis and Gage, 1999; van Praag et al. 2002). It is hypothesized that newborn neuronal cells arise from stem cells in the adult brain. NSCs are the self-renewing multipotent cells that generate the main phenotypes of the nervous system, neurons, astrocytes and oligodendrocytes; as such they hold the potential to treat a broad range of CNS diseases and injuries (Mckay, 1997). Neural progenitor and stem cells have been isolated and characterized *in vitro* from the adult brain, further supporting the existence of NSCs in the adult CNS (Reynolds and Weiss, 1992; Gage et al. 1995). The existence of NSCs in the adult brain has tremendous consequences for cellular therapy in the CNS, but also for our understanding of developmental biology (Taupin, 2006a).

Depression is a major public health problem that affects 12–17% of the population (Kessler et al. 1994). Various classes of drugs are currently prescribed for the treatment of depression (Wong and Licinio, 2001; Brunello et al. 2002). Among them selective serotonin reuptake inhibitors (SSRIs), like fluoxetine, monoamine oxidase inhibitors (MAOIs), like tranylcypromine, specific norepinephrine reuptake inhibitors (SNRIs), like reboxetine and phosphodiesterase-IV inhibitors, like rolipram, alleviate symptoms of depression. It is hypothesized that an imbalance in serotonin (5-hydroxytryptamine or 5-HT) and noradrenaline (NA) pathways may underlie the pathogenesis of depressive disorders (Hindmarch, 2001; Owens, 2004). SSRIs, like fluoxetine, may produce their therapeutic effects by increasing brain levels of 5-HT, a neurotransmitter implicated in the modulation of mood and anxiety-related disorders (Whittington et al. 2004; Ryan, 2005). Among the 5-HT receptor subtypes, the 5-HT1A receptor has been prominently implicated in the modulation of mood and anxiety-related disorders (Gross et al. 2002). There are increasing evidences that the hippocampus, a structure classically involved in leaning and memory, is involved in the modulation of emotional responses, particularly depression. Clinical magnetic resonance imaging and post-mortem studies in depression patients, as well as in animal studies, reveal that chronic stress and depression result in loss of nerve cells and atrophy in the hippocampus, and that these effects can be reversed by antidepressants (Watanabe et al. 1992a; Sheline et al. 1996; Czeh et al. 2001; Campbell et al. 2004; Videbech and Ravnkilde, 2004; Colla et al. 2006).

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This suggests that neurogenesis may be an underlying factor in the contribution of the hippocampus to depression. In support of this contention, glucocorticoids, stress-related hormones, induce brain atrophy (Sapolsky, 2000; McEwen, 2001) and decrease neurogenesis (Gould et al. 1991; Cameron and Gould, 1994), whereas antidepressants, like fluoxetine, promote neurogenesis (Malberg et al. 2000; Malberg and Duman, 2003). Investigators have aimed at confirming and unraveling the mechanism underlying the involvement of adult neurogenesis to the etiology of depression.

Neurogenesis Contributes to the Therapeutic Effects of Antidepressants

The effect of antidepressants, like fluoxetine, tranylcypromine, reboxetine and rolipram, on adult neurogenesis was assessed by means of bromodeoxyuridine (BrdU) labeling, immunohistochemistry for neuronal specific markers and confocal microscopy (Malberg et al. 2000, 2004). BrdU is a thymidine analog that incorporates into the DNA of dividing cells and is used for birthdating cells and monitoring cell proliferation (Miller and Nowakowski, 1988; Kuhn et al. 1996; Taupin, 2006b). Chronic administration of these antidepressants increases neurogenesis in the DG, but not the SVZ in adult rats, suggesting that hippocampal neurogenesis contributes to the therapeutic effects of antidepressants (Malberg et al. 2000, 2004).

To study the functional implication of such observations, Santarelli et al. (2003) aimed at characterizing whether an increase in neurogenesis is required for the effect of antidepressants. X-ray irradiation of the hippocampal area in adult rats causes long-term reductions in cell proliferation in the DG (Tada et al. 2000). Hippocampal x-ray irradiation, but not irradiation of other brain areas, like the SVZ or the cerebellar region, prevented the neurogenic effect of antidepressants, like fluoxetine, in adult mice (Santarelli et al. 2003). The behavioral effect of the antidepressants on the novelty-suppressed feeding (NSF) test was also abolished after hippocampal irradiation. The NSF test, in which animals are food deprived, then placed into a novel environment containing food, and assessed for the latency to begin eating, is devised to assess chronic antidepressant efficacy in rodents (Bodnoff et al. 1988). Further, 5-HT1A receptor null mice were insensitive to the neurogenic and behavioral effects of fluoxetine. In all, these data show that SSRIs, like fluoxetine, increase hippocampal neurogenesis, which contributes to their behavioral effects (Santarelli et al. 2003).

A Neurogenic Theory of Depression

Stress, an environmental factor, is an important causal factor in precipitating episodes of depression in human, and potently suppresses hippocampal neurogenesis in adult monkey (Gould et al. 1998; Malberg and Duman, 2003), probably due to increased glucocorticoid release (Gould et al. 1991; Cameron and Gould, 1994). Neurogenesis plays an important role in biology of depression; particularly the stimulation of neurogenesis by antidepressants contributes to their behavioral effects (Malberg et al. 2000; Santarelli et al. 2003). It is proposed that stress-induced decrease of neurogenesis in the DG is an important causal factor in precipitating episodes of depression. The waning and waxing of neurogenesis in the hippocampal formation are therefore important causal factors, respectively, in the precipitation of, and recovery from, episodes of clinical depression, probably mediated through the increase in brain serotonin levels (Jacobs et al. 2000).

The mechanism underlying the increased neurogenesis mediated by antidepressants remains to be identified. Studies reveal that the 5-HT, particularly 5-HT1A, receptor subtypes mediate the involvement of adult neurogenesis in depression (Banasr et al. 2004), and that fluoxetine targets a population of early progenitor cells in the DG, rather than stem-like cells in the DG (Encinas et al. 2006). The effect of antidepressants on neurogenesis may be mediated by trophic factors, like brain-derived neurotrophic factor (BDNF). On the one hand, antidepressant treatments increase the level of expression of BDNF in the patents' brain, and BDNF has an antidepressant effect (Siuciak et al. 1997; Chen et al. 2001; Saarelainen et al. 2003). On the other hand, administration of BDNF increases adult neurogenesis in the hippocampus (Scharfman et al. 2005). This suggests that the effect of antidepressants on neurogenesis may be mediated by BDNF, through its signaling pathway, particularly the mitogen-activated protein (MAP) kinase pathway (Duman et al. 2006). The MAP kinase pathway is a BDNF signaling cascade mediated

by the activation of MAP kinase (MAPK) that phosphorylates and activates the extracellular signal-regulated kinase (ERK) pathway (Huang and Reichardt, 2003). A hypothesis supported by recent findings showing that exercise promotes hippocampal neurogenesis, BDNF expression, and has an antidepressant effect (van Praag et al. 1999; Eadie et al. 2005; Russo-Neustadt and Chen, 2005; Bjornebekk et al. 2005; Ernst et al. 2006). Though these studies provide compelling evidences of the role of BDNF in depression and neurogenesis, it remains to link the activity of BDNF on the increase of neurogenesis mediated by antidepressants.

There are however controversies and debates over the involvement of the hippocampus and adult neurogenesis in the etiology of depression. Among them, i) a link between neurogenesis, loss of nerve cells, atrophy and decrease of hippocampal volume in depression subjects is yet to be demonstrated, ii) studies show that hippocampal volume remains unchanged in depressive patients (Axelson et al. 1991; Inagaki et al. 2004; Bielau et al. 2005), iii) the hippocampal formation may not be primarily involved in depressive episodes, as other areas of the brain may play a critical role in depression (Nestler et al. 2002; Ebmeier et al. 2006), iv) there are questions over validity of animal models of depression as representative of the human disorder, and v) neurogenesis may be more a contributing factor of CNS plasticity, rather than to specific physiological or pathological processes (Taupin, 2006c). The involvement of adult neurogenesis in depression remains therefore speculative (Feldmann et al. 2006).

In all these data involved the hippocampus, a structure classically involved in leaning and memory, and adult neurogenesis in depression and anxiety disorders (Thomas and Peterson, 2003). Antidepressant treatments may increase neural plasticity and adult neurogenesis, especially in the hippocampus. However, the neurogenic theory of depression remains the source of debates and controversies, and to be further confirmed (Feldmann et al. 2006). More data and evidences are needed to confirm the involvement of adult neurogenesis in depression.

Conclusion

These studies show that antidepressants increase hippocampal neurogenesis, and establish a causal relation between the stimulation of neurogenesis and the effect of antidepressants. New neuronal cells that survived and integrate the pre-existing network survive for long period, over two years in human (Eriksson et al. 1998). Therefore, antidepressants may have long-term consequence on the architecture, and functioning of the CNS. The function of newly generated neuronal cells in the adult brain remains the source of intense research and debates. Though the hippocampus and neurogenesis play an important role in depression, these data remain the source of controversies and debates, and the involvement of adult neurogenesis in the etiology of depression to be further characterized. Nonetheless, the evidence that stimulation of neurogenesis contributes to the effects of antidepressants may hold the key for the understanding of the long-term consequences of the effects of antidepressants of the physiopathology of the CNS, and lead to new drugs design, and new strategies to treat depressive disorders. To this aim, determining the cellular and molecular mechanisms of action of antidepressants on neurogenesis will be a determining factor.

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