

# Dentate gyrus neurogenesis and depression

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**Abstract:** Major depressive disorder (MDD) is a debilitating and complex psychiatric disorder that involves multiple neural circuits and genetic and non-genetic risk factors. In the quest for elucidating the neurobiological basis of MDD, hippocampal neurogenesis has emerged as a candidate substrate, both for the etiology as well as treatment of MDD. This chapter critiques the advances made in the study of hippocampal neurogenesis as they relate to the neurogenic hypothesis of MDD. While an involvement of neurogenesis in the etiology of depression remains highly speculative, preclinical studies have revealed a novel and previously unrecognized role for hippocampal neurogenesis in mediating some of the behavioral effects of antidepressants. The implications of these findings are discussed to reevaluate the role of hippocampal neurogenesis in MDD.

**Keywords:** dentate gyrus; depression; neurogenesis; serotonin; antidepressants; hippocampus

## Introduction

Understanding the neurobiological basis of major depressive disorder (MDD) is one of the most pressing challenges for today's society. Severe forms of depression affect 2–5% of the U.S. population, and mood disorders impact 7% of the world's population and rank among the top ten causes of disability (Murray and Lopez, 1996). The diagnosis of MDD based on the criteria established by the *Diagnosics and Statistical Manual of Mental Disorders* (American Psychological Association, 2000) includes the persistence of depressed mood, low self esteem, feelings of hopelessness, decreased

ability to concentrate, diminished interest in pleasurable activities, daily insomnia or hypersomnia, weight loss or gain, and recurrent suicidal ideation. The diagnostic criteria for MDD convey the complexity of the disease and suggest that multiple neural circuits subserving distinct cognitive and affective processes are likely to be involved.

Our comprehension of the mechanisms underlying the pathogenesis of MDD has evolved considerably since the formulation of the monoamine hypothesis (Bunney and Davis, 1965; Schildkraut, 1965; Nestler et al., 2002). The recent emphasis on neural circuits as opposed to a chemical imbalance catalyzed a fundamental shift in our conceptualization of MDD and psychiatric disorders. It provided a framework to understand how genes, through their effects on neural circuits, influence our ability to encode experience and adapt to environmental stimuli and stressors. Implicit in this idea is that genes moderate vulnerability to the

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effects of environmental stress during particularly sensitive or critical periods in brain development by determining the optimal range of neuronal circuit function for the organism. Indeed, the neurotrophic, neuroplasticity and network hypotheses of MDD all reflect the biology of gene products in the context of synaptic and structural plasticity of neural circuitry (Duman et al., 1997; Duman, 2002; Nestler et al., 2002; Castren, 2005).

Dentate gyrus neurogenesis has gained considerable attention as both a form of structural plasticity and as a neural substrate for the pathophysiology of MDD. The neurogenic hypothesis posits that a decrease in the production of newborn dentate granule cells in the hippocampus causally relates to the pathogenesis and pathophysiology of MDD and that enhanced neurogenesis is necessary for treatment of depression (Duman et al., 2000; Jacobs et al., 2000). The hypothesis, when first proposed, was predicated on the following observations, which are reviewed in greater detail in subsequent sections. First, stress, which is widely recognized as a major causal factor in MDD, is known to suppress neurogenesis. Second, most antidepressant (AD) treatments increase hippocampal neurogenesis. Third, imbalance in the serotonin system influences hippocampal neurogenesis. Fourth, the induction of neurogenesis is contingent upon chronic but not subchronic (acute) selective serotonin reuptake inhibitor (SSRI) treatment, paralleling the time course for therapeutic actions of ADs. Finally, the therapeutic lag in the response to SSRIs in patients with MDD mirrors the timeline of maturation and integration of newborn dentate granule cells. Consequently, the dentate gyrus and neurogenesis therein are potential substrates for the AD response.

Central to the neurogenic hypothesis is the assumption that the dentate gyrus plays an important role in mediating cognitive and affective processes. Moreover, since levels of neurogenesis change during the lifetime of the organism, changes in dentate neurogenesis may contribute to dentate gyrus function in different ways. Another assumption is that neurogenesis represents a potentially adaptive mechanism or form of plasticity. Deficits in neurogenesis during critical

periods in brain development could, therefore, be pathogenic in that they profoundly impact the trajectory of emotional development. Deficits in adult hippocampal neurogenesis could compromise hippocampal-dependent functions and contribute to the pathophysiology of MDD.

In this chapter, we focus on hippocampal neurogenesis as it relates to MDD. Our aim is to distill the observations made in the rapidly growing field of hippocampal neurogenesis and to critically assess the putative role of neurogenesis in the etiology and treatment of MDD. We begin by defining a framework for the reader to understand how neurogenesis can contribute to dentate gyrus function. Within this framework, we will first evaluate evidence for deficits in hippocampal neurogenesis in patients with MDD. We will then examine the role of the serotonergic system in hippocampal neurogenesis because the best characterized genetic risk alleles for MDD encode components of this system. Because susceptibility to MDD conferred by genes is likely to be revealed by environmental risk factors such as stress, we will discuss the relationship between stress and neurogenesis. We then review the considerable evidence linking the effects of ADs with increased hippocampal neurogenesis. Finally, we will turn to evidence provided by studies using preclinical models that attempt to establish a causal link between hippocampal neurogenesis and the etiology, and pathophysiology of MDD and the requirement for neurogenesis in mediating the behavioral effects of ADs.

## Neurogenesis and MDD

### *A general framework for neurogenesis and dentate gyrus function*

Since the seminal findings of Altman and Das in 1965, it is now well accepted that the adult hippocampus is host to the birth and integration of newborn dentate granule cells in the dentate gyrus (Altman and Das, 1965). In the rat, the species for which the best data are available, it is estimated that 9000 new cells are born each day in the DG, and, of these, approximately 50% go on to express

neuron-specific markers. At this rate, the number of new granule neurons born each month is equal to 6% of the mature granule cell population (Cameron and McKay, 2001). In non-human primates, the rate of neurogenesis may be lower than the rate documented in rodents (Kornack and Rakic, 1999; Gould et al., 1999b). One should bear in mind that these data reflect neurogenesis under laboratory housing conditions, and given the increase in neurogenesis with environmental enrichment (Kempermann et al., 1997; Gould et al., 1999a), could underestimate the rates of neurogenesis in the normal habitat. Likewise, rates of neurogenesis in man maybe underestimated by available data, because human data were based on a single study in which tissue samples were taken from cancer patients injected with a mitotic marker, bromo-deoxyuridine (BrdU) before death (Eriksson et al., 1998). The number of BrdU-labeled neurons entering the neuronal lineage was lower than that reported for marmosets and rodents, but the age of subjects could explain the difference because they were old, and neurogenesis declines with age (Seki and Arai, 1995; Kuhn et al., 1996; Rao and Shetty, 2004). Therefore, it is unclear to what extent the relatively low level of neurogenesis observed in the human subjects was due to real species difference.

The study of adult hippocampal neurogenesis has revealed it to be a robust phenomenon that is capable of conferring previously unrecognized forms of plasticity to the dentate gyrus. For example, it is clear that both net addition of newly generated neurons and replacement of mature cells occur in the adult dentate gyrus and that the extent to which these processes occur may vary with the animals age, and environmental and physiological parameters (Bayer et al., 1982; West, 1993; Kempermann et al., 1998; Nottebohm, 2002; Amrein et al., 2004; Wiskott et al., 2006). Modeling and computational approaches have revealed merits of both net addition and replacement in optimizing hippocampal network function (Chambers et al., 2004; Becker, 2005; Meltzer et al., 2005; Wiskott et al., 2006). Figure 1 illustrates the distinct, but potentially interrelated, ways by which neurogenesis can modify the cellular composition of the dentate gyrus.

1. Increase the number of mature dentate granule cells  
The integration of newborn neurons can result in an increase in the granule cell layer of the dentate gyrus. It is conceivable that a net increase in size is possible only within a certain period in an animal's life. An increase in cell number can result from an enhancement in the rate of proliferation or the percentage of newborn neurons that survive.
2. Provide a reservoir of highly plastic immature neurons in the adult dentate gyrus  
Newly generated dentate granule cells also exhibit forms of synaptic plasticity distinct from those of mature cells in the adult hippocampus. Newborn dentate granule cells show unique physiological properties such as lower thresholds for induction of long-term potentiation and long-term depression than do mature neurons (Schmidt-Hieber et al., 2004; Song et al., 2005). Moreover, newborn dentate granule cells, unlike mature granule cells, are able to undergo LTP under conditions of increased GABAergic inhibition (Wang et al., 2000; Snyder et al., 2001; Saxe et al., 2006). Thus, in addition to conferring structural plasticity to the dentate gyrus, neurogenesis also creates a transient reservoir of excitable, highly plastic cells that may serve a unique biological function, distinct from that of mature granule neurons. The size of such a reservoir can be influenced by numerous physiological and environmental factors and contingencies.
3. Generate multiple cell types in the dentate gyrus  
While it is widely agreed that neurogenesis in the subgranular zone (SGZ) results in generation of dentate granule cells, there is one report showing that GABAergic basket cells in the dentate gyrus incorporate BrdU and form functional inhibitory synapses with dentate granule cells (Liu et al., 2003). Thus, it is plausible that the generation of interneurons may occur under certain conditions to influence network activity. Clearly more evidence is needed to support this possibility. In addition to the generation of neurons in

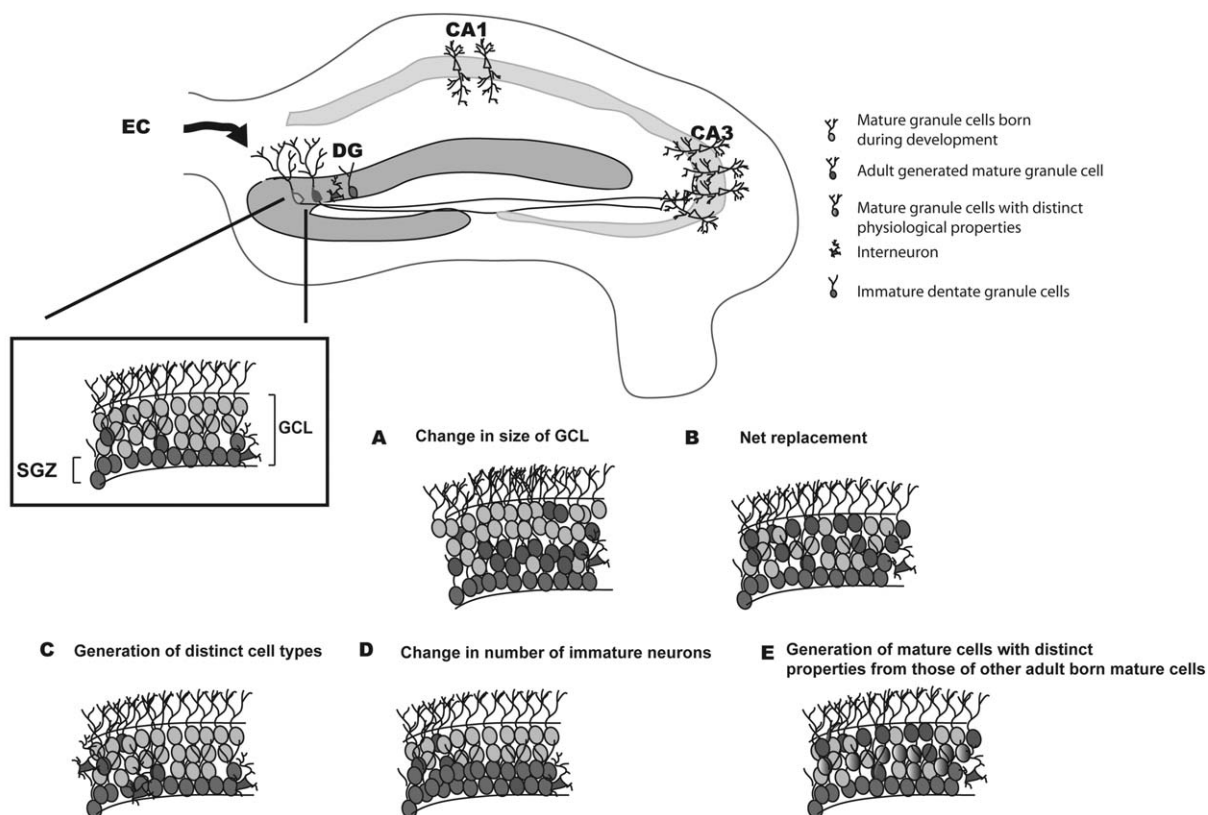


Fig. 1. A schematic of the dentate gyrus granule cell layer (GCL) illustrating the different ways by which neurogenesis can influence its structure and function. Boxed panel reveals a cross section of the dentate GCL with the different populations that reside within it: mature granule cells born during development (light blue), adult-generated mature granule cells (dark blue), adult-born immature neurons (red) and interneurons (green). Over the lifespan, the GCL may increase in size due to a net addition of new neurons (A) or may remain unchanged due to a net replacement of developmentally generated granule cells (B). Changes in neurogenesis can result in increased representation of interneurons (C), a larger pool of adult generated immature neurons (D) or the generation of mature neurons with distinct physiological and biochemical properties (E). Conceivably, neurogenesis may be altered in any one of these ways in MDD. Conversely, AD drugs may influence DG function in more than one way to exert their behavioral effects. (See Color Plate 38.1 in color plate section.)

the dentate gyrus, proliferation in the SGZ also generates glial cells. The emerging role for glial cells in modulating synaptic function in health and disease underscores the need to understand how newly generated glial cells contribute to hippocampal physiology and function (Ma et al., 2005; Haydon and Carmignoto, 2006).

#### 4. Drive turnover and replacement of mature dentate granule cells

The integration of newborn neurons can occur to replace the death of mature neurons.

Such a mechanism, when predominant, would not increase the size of the dentate gyrus but ensure replacement of cells, whose functions are impaired, and rejuvenate the network with new cells (Nottebohm, 2002). There is some evidence to suggest that adult-generated mature dentate granule cells, while sharing electrophysiological properties with their early-development-born counterparts, exhibit greater plasticity in response to behaviorally relevant stimuli (Laplagne et al., 2006; Ramirez-Amaya et al., 2006).

Independent of the balance between the integration of new neurons and the death of mature neurons, it is conceivable that a specific form of experience can result in a larger representation of specific granule cells selected for by that kind of experience. Such a representation may manifest in a distinct pattern of biochemical and electrophysiological properties found in one cohort of newborn cells versus another. Functional heterogeneity within the hippocampus and dentate gyrus supports the possibility that subsets of neurons within different regions of the dentate gyrus could reflect distinct experiences (Moser and Moser, 1998; Scharfman et al., 2002; Silva et al., 2006).

The aforementioned ways by which neurogenesis contributes to the structure and function of the dentate gyrus convey the complexity of the phenomenon of hippocampal neurogenesis. They also remind us of the many ways by which neurogenesis may be altered in pathological conditions.

### ***Hippocampal dysfunction and atrophy in MDD***

Hippocampal dysfunction in MDD is well supported by clinical studies which have shown that MDD is often accompanied by deficits in declarative learning and memory and diminished cognitive flexibility that are dissociable from changes in motivation (Austin et al., 2001; Fossati et al., 2002). The anatomical and functional segregation of the hippocampus along its septotemporal axis suggests roles for the hippocampus in both cognitive and emotional processes (Moser and Moser, 1998; Strange and Dolan, 1999; Strange et al., 1999; Bannerman et al., 2003). As a first step to thinking about the contribution of the dentate gyrus and dentate neurogenesis to the pathophysiology of MDD, one must consider the direct evidence for hippocampal dysfunction and atrophy in MDD.

While longitudinal studies linking changes in hippocampal structure and function with the etiology of depression are lacking, we have made progress in identifying changes in hippocampal function, cellular structure and volume that are associated with pathophysiology of depression. Direct measurements of hippocampal function in

the depressed brain are made using neuroimaging techniques such as positron emission tomography (PET), a powerful way of identifying neural structures with altered metabolic activity. Studies on patients with MDD have revealed alterations, but only in a very small number of studies and with conflicting results. This is partly due to the limited resolution of PET. Using cerebral blood flow PET, one group reported increased blood flow in the hippocampus of acutely depressed patients with a short duration of illness (Videbech et al., 2001, 2002; Videbech and Ravnkilde, 2004). By contrast, two other studies have shown either a decrease or no change in metabolism in the hippocampus of patients with MDD using fluorodeoxyglucose (FDG)-PET imaging (Saxena et al., 2001; Drevets et al., 2002; Kimbrell et al., 2002). Differences in patient profile with regards to severity and duration of illness and treatment could explain these differences. Alternatively, it has been suggested that increased activity, if untreated, may result in hippocampal atrophy and decreased metabolism. Atrophy would occlude detection of changes in activity.

A consistent finding that has emerged from magnetic resonance imaging (MRI) studies on patients with MDD is a reduction in hippocampal volume. Despite a few studies that failed to report any differences between patients with MDD and control groups using MRI, there is consensus for reduced hippocampal volume in MDD (Sheline, 1996; Sheline et al., 1999; Bremner et al., 2000; von Gunten et al., 2000; Vakili et al., 2000; Neumeister et al., 2005). Two recent meta-analyses of studies measuring temporal lobe structures in MDD compellingly demonstrate a reduction in hippocampus in people with recurrent depression relative to age- and sex-matched controls (Campbell et al., 2004; Videbech and Ravnkilde, 2004). Interestingly, frequency of depressive episodes and the duration for which depression is untreated correlate with magnitude of reduction in hippocampal volume (MacQueen et al., 2003; Sheline et al., 2003). Taken together, the evidence argues for reduced hippocampal volume in MDD and that such changes are likely to be a result of depression rather than a cause. However, it is worth mentioning here that a smaller hippocampus is



thought to be a predisposing factor for, rather than a consequence of, post-traumatic stress disorder (Gilbertson et al., 2002).

The significance of hippocampal volume change in the context of cognitive deficits is conveyed by a recent study that shows that healthy individuals who complained of memory impairments had smaller hippocampal volumes than non-impaired controls (van der Flier et al., 2004). Another study showed a correlation between deficits in recollection memory performance and reduced hippocampal volume in elderly depressed patients (von Gunten and Ron, 2004). However, these studies are limited in number and comprised elderly individuals who are likely to have other brain changes that may contribute to the memory impairments.

Changes in hippocampal volume can be explained by several different mechanisms that may operate in concert at the cellular and circuit levels including: (i) Increased apoptosis of mature neurons or glial cells. (ii) A loss of neuropil which may involve changes in dendritic complexity, spine density, and number and size of afferent and efferent axonal projections. (iii) Reduced neurogenesis or gliogenesis in the SGZ of dentate gyrus. The link between neurogenesis and hippocampal volume has been addressed in histological analyses of postmortem tissue obtained from brains of patients with MDD, and will be discussed next.

### ***Neurogenesis and cell death in MDD***

Pathohistological studies of postmortem tissue of patients, while small in number, have provided some clues about the nature of cellular changes in the hippocampus of a depressed individual. One study examined synaptic density and glial cell number using synaptophysin and GFAP-immunoreactivity, respectively, and found no differences in the hippocampus of medicated patients with MDD relative to controls (Muller et al., 2001). Another study revealed low levels of apoptosis in the dentate gyrus, CA1, CA4, subiculum and entorhinal cortex of patients with MDD (Lucassen et al., 2001). A third study showed a significant increase in cell density of granule and glial cells in the

dentate gyrus and pyramidal neurons and glial cells in the CA fields (Stockmeier et al., 2004). In addition, the authors reported a reduction in soma size of pyramidal neurons and a trend towards the same in dentate granule cells. Finally, one group directly examined the proliferation of cells in the adult dentate gyrus of MDD patients using an M-phase marker, Ki-67 (Reif et al., 2006). Their results showed no changes in Ki-67 immunopositive cells in hippocampus of depressed patients. While this study is informative and is the first to estimate levels of proliferation in the MDD brain, it must be interpreted with several caveats in mind. First, a reduction in neurogenesis in patients with MDD could be masked by AD-mediated increase in cell proliferation. Second, and for obvious reasons, the study could not measure changes in survival of newborn cells or examine the kinetics of turnover and maturation of newborn dentate granule cells.

The pathohistological analyses suggest that changes in neuropil, rather than neurogenesis, may account for reductions in hippocampal volume. Indeed, the effects of stress on hippocampal white matter are well documented. Preclinical studies have shown that volumetric changes result from reduced dendritic complexity and not ablation of hippocampal neurogenesis (Santarelli et al., 2003; McEwen, 2005). It should be noted that while these data argue against the possibility that reduced cell number owing to extensive cell death or decreased neurogenesis is a primary mediator of hippocampal volume change, they do not directly address the possibility that neurogenesis is altered in MDD. Since most of the patients were on medication at the time of death, and since AD drugs potently upregulate hippocampal neurogenesis, it is possible that depression-related alterations in neurogenesis could have been masked in these studies. Moreover, since hippocampal neurogenesis in humans is likely to change with age, small differences in proliferation or survival of newborn neurons in postmortem analyses of older patients could be difficult to detect. Further studies on postmortem tissue of medicated and non-medicated individuals are needed to identify specific changes in hippocampal neurogenesis associated with MDD.

## Genes, environment and MDD

Depression is a complex and multifactorial illness with genetic and non-genetic underpinnings. The heritability of MDD is likely to be in the range of 40–50% and there is substantial evidence to suggest that the phenotypic expression of MDD is contingent upon interactions between the genetic make-up of the individual and environmental factors, an interaction that has a dramatic effect on the formation and functioning of neural circuitry (Sullivan et al., 2000; Kendler et al., 2001; Caspi and Moffitt, 2006; Leonardo and Hen, 2006; Levinson, 2006). Here, it must be emphasized that human susceptibility to MDD as revealed by environmental factors is tremendously magnified in early life. For example, adults who had experienced four out of seven traumatic events in early life had a 4.6-fold increased risk of developing depressive symptoms later in life and were 12.2-fold more likely to commit suicide (Felitti et al., 1998; Chapman et al., 2004). These studies underscore the idea of a critical period in “emotional development” when mechanisms mediating neural circuit synaptic- and structural plasticity are particularly susceptible to environmental input, and if compromised by a vulnerability conferred by genes, can result in maladaptive alterations in neural circuit function and pathological behavior. While the search for candidate genes for MDD has yielded some convergence from linkage studies that certain genetic loci are involved, more data are clearly needed to conclusively implicate a specific gene in the etiology of MDD. A notable exception is the serotonin transporter (5-HTT) polymorphism. In a landmark study, Caspi and colleagues found that a functional polymorphism in the 5-HTT gene moderated the sensitivity of individuals to the depressogenic effects of early life stress, a finding recently replicated by Kendler and colleagues (Caspi et al., 2003; Kendler et al., 2005). Caspi and colleagues found that people who carried one or two copies of the “short” allele of 5-HTT, associated with lower levels of 5-HTT and impaired reuptake of serotonin (5-HT) at synapses, had more depressive symptoms and suicidal behavior in relation to stressful life events than did people who had the “long allele”.

Importantly, the association between the 5-HTT polymorphism and depression is only observed in individuals who had experienced significant stressful life events. These findings argue that the serotonergic system has a critical influence on neurodevelopmental processes that lead to MDD. If hippocampal neurogenesis is to be considered as a candidate neural substrate for depression, then the effects of serotonergic dysregulation on it warrants comment. The following section addresses the role of the serotonergic system in modulating dentate gyrus structure and function.

### *The 5-HT system and hippocampal neurogenesis*

Serotonergic terminals originating from the dorsal raphe nucleus (DRN) and median raphe nuclei (MRN) diffusely innervate multiple structures in the vertebrate forebrain and reach the ventricles via the supra-ependymal plexus (Azmitia and Segal, 1978; Freund et al., 1990). The serotonergic innervation of the hilus, molecular layers of the dentate gyrus and the SGZ supports the possibility that 5-HT signaling may influence adult neurogenesis (Oleskevich et al., 1991). The idea that serotonin can influence neurogenesis was first proposed three decades ago (Lauder and Krebs, 1978). However, the specific ways by which the 5-HT system influences adult dentate neurogenesis was established only relatively recently. The first studies to address the role of 5-HT in adult hippocampal neurogenesis used serotonin depletion analyses. Injection of the serotonin neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) or 5-HT synthesis inhibitor parachlorophenylalanine (PCPA) into the raphe of young female rats resulted in a reduction of dentate granule cell proliferation and the number of immature neurons as assessed by BrdU uptake and PSA-NCAM immunostaining, respectively (Brezun and Daszuta, 1999, 2000). Moreover, the same group showed that they could rescue the deficit in hippocampal proliferation in these rats following intrahippocampal grafts of embryonic 5-HT neurons (Brezun and Daszuta, 2000). A potential role for 5-HT in influencing the maturation of dentate granule cells comes from studies in which rat pups were treated

with phenylchloromethamphetamine (PCA) or 5,7-DHT to reduce serotonergic innervation of the forebrain. Analysis of dentate granule cells in rodents with reduced serotonergic innervation revealed fewer dendritic spines and synapses, but otherwise normal dendritic complexity (Yan et al., 1997; Faber and Haring, 1999), suggesting that serotonergic signaling is important for selected, and not all, aspects of the neuronal maturation process. While the limitations inherent to these pharmacological lesion studies must be acknowledged, these studies illustrate how deficits in the 5-HT system can have consequences for the maturation of dentate granule cells. Given the striking recapitulation in adult neurogenesis of the early-developmental neuronal maturation process, it is likely that changes in 5-HT signaling have similar consequences on neurons born in adulthood (Esposito et al., 2005; Laplagne et al., 2006; Overstreet-Wadiche and Westbrook, 2006). Indeed, the well-characterized effects of 5-HT receptor agonist and antagonists and SSRIs on adult neurogenesis (Malberg et al., 2000) solidify the link between 5-HT and adult hippocampal neurogenesis. Importantly, studies on 5-HT receptors, which are discussed next, offer a glimpse into the ways by which altered serotonin levels as a consequence of a genetic polymorphism, such as the 5-HTT polymorphism, can influence the birth and maturation of newborn dentate granule cells.

The effects of 5-HT levels on neurogenesis reflect the sum of interactions between the synthesis of 5-HT, its release and its actions at different 5-HT postsynaptic receptors acting in both a cell autonomous and non-cell autonomous manner. The effects of 5-HT on a newborn neuron depend on the repertoire of 5-HT receptors that it expresses. Since the maturation of newborn neurons is intimately connected with the activity of the network, it is also influenced by the actions of different 5-HT receptors expressed within the hippocampal formation in interneurons, mature dentate granule cells and afferent projections arising in the entorhinal cortex. The 5-HT<sub>1A</sub> receptor (5-HT<sub>1AR</sub>) is the best-studied 5-HT receptor in the context of adult hippocampal neurogenesis. Acute administration of 5-HT<sub>1A</sub> antagonists results in decreased cell proliferation in the adult

dentate gyrus (Radley and Jacobs, 2002). Consistent with these findings, acute or chronic treatment with the 5-HT<sub>1A</sub> agonist 8-OH DPAT increases proliferation in the SGZ and the number of adult born neurons (Santarelli et al., 2003; Banasr et al., 2004). The effects of activating 5-HT<sub>1AR</sub> appear to be restricted to proliferation and do not affect the differentiation of newborn progenitors into neurons or glial cells. The increase in proliferation could reflect a change in rate of progression through the cell cycle or an increase in the size of the proliferative pool in the SGZ. It is unclear, given the experimental design employed in these studies, whether activation of 5-HT<sub>1AR</sub> also influences the survival of newborn neurons. Interestingly, mice lacking the 5-HT<sub>1AR</sub> fail to respond to the neurogenic effects of chronic fluoxetine (Santarelli et al., 2003).

Two other 5-HT receptors, the 5-HT<sub>2A</sub> and 5-HT<sub>1B</sub> receptors, have also been implicated in cell proliferation in the adult SGZ. While neither 5-HT<sub>1B</sub> agonists nor antagonists affect baseline cell proliferation, the former can, however, restore normal levels of proliferation in PCPA pretreated rats. These data suggest that effects of the 5-HT<sub>1B</sub> receptor on cell proliferation are small under physiological conditions, but can become important when 5-HT levels are decreased. The pharmacology of the 5-HT<sub>2A</sub> receptor is also complex. 5-HT<sub>2A</sub> antagonists decrease cell proliferation but agonists have no effect (Banasr et al., 2004), suggesting that under physiological conditions, the 5-HT<sub>2A</sub>-dependent signaling pathways that modulate neurogenesis may be saturated. Taken together, these observations reveal the differential effects of recruiting different postsynaptic 5-HT receptors on hippocampal neurogenesis.

Central to understanding how changes in 5-HT levels influence neurogenesis is knowledge of the expression of different 5-HT receptors in neural progenitors and at different stages of their maturation. Conspicuously absent from the pharmacological studies is precise information for 5-HT receptor distribution in the adult SGZ. The 5-HT<sub>1AR</sub> is an exception to the rule. We know that the 5-HT<sub>1AR</sub> is expressed at very low levels, if any, in the SGZ of the rodent hippocampus.



In both rat and mouse, 5-HT<sub>1A</sub>R expression is restricted to the mature dentate granule cells rather than the immature population of cells during development of the dentate gyrus (Patel and Zhou, 2005; Sahay and Hen, unpublished data). The effect of 5-HT<sub>1A</sub>R agonists on cell proliferation is, therefore, likely to be non-cell autonomous. It is possible that the 5-HT<sub>1A</sub>R is required in hilar interneurons or mature dentate granule cells to mediate the effects of 5-HT on cell proliferation. Cell-type specific ablation and overexpression of the 5-HT<sub>1A</sub>R will reveal its precise contribution in different cell types to adult hippocampal neurogenesis.

The specific role of different 5-HT receptors in the maturation and integration of newborn neurons is still to be elucidated. It is also unclear how 5-HT may impact the turnover of mature dentate granule cells or influence the survival of newborn dentate granule cells. The role for distinct 5-HT receptors in regulation of developmental processes such as dendritic development, synaptogenesis and glutamate receptor trafficking (Kondoh et al., 2004; Kvachnina et al., 2005; Yuen et al., 2005a, b) suggests that 5-HT receptor-dependent mechanisms during development may be conserved in neurogenesis in the adult brain depending on which 5-HT receptors are expressed and when during neuronal maturation. In addition, 5-HT signaling can induce the production of neurotrophins and growth factors known to regulate hippocampal neurogenesis.

### ***The role of stress in MDD and its effects on neurogenesis***

Stressful life experiences play a pivotal role in development of MDD in individuals with a genetic vulnerability (Holsboer and Barden, 1996; Gold and Chrousos, 2002). Major stressors precede the appearance of the first symptoms, and dysregulation of the hypothalamic-pituitary-adenocortical (HPA) system is often observed in patients with MDD (Carroll et al., 1968a). An optimally functional HPA system enables the organism to respond appropriately to stressful stimuli by controlling the production of adrenal steroids,

the glucocorticoids, which mobilize energy, increase cardiovascular tone and influence immune and nervous system functions. In response to a stressful event, for example, a neuroendocrine cascade is initiated in which corticotropin releasing hormone (CRH) is released from neurons in the paraventricular nucleus (PVN) in the hypothalamus, which then triggers release of corticotropin by the anterior pituitary to stimulate glucocorticoid secretion by the adrenal cortex. A hyperactive HPA, on the other hand, results in the oversecretion of glucocorticoids with deleterious consequences for the physiology of the viscera and brain (Sapolsky, 2000). In addition, increased glucocorticoid levels can impair serotonergic signaling (Joels and van Riel, 2004). It is therefore not surprising that the stress response is tightly regulated by efferents from multiple brain regions that converge onto the PVN, where incoming information is integrated to elicit an adaptive response. Afferent inputs of the PVN are inhibitory or facilitative in nature and arise in brain stem nuclei, amygdala, cortex, septum and the hippocampus, and are in turn regulated by a negative feedback system. The hippocampus, for example, exercises a powerful inhibitory influence on HPA function to terminate the stress response, and is in turn regulated by glucocorticoids acting on cognate receptors expressed within the hippocampal formation. Dysregulation of such control can, therefore, result in hypersecretion of glucocorticoids and an exaggerated stress response that can severely impact neural circuit function. Consistent with preclinical findings, about half of all depressed patients show a blunted response to the dexamethasone suppression test (Carroll et al., 1968b; Holsboer et al., 1982), which measures the ability of an exogenous glucocorticoid receptor agonist to suppress endogenous stress hormone release. Moreover, patients with MDD show elevated levels of CRH in the cerebrospinal fluid, increased numbers of CRH containing cells in the PVN, and decreased CRH binding in the prefrontal cortex. Thus, the optimal function of the hippocampal formation is a critical factor in modulation of the stress response, and an exaggerated stress response can, in turn, negatively impact hippocampal function.

One effect of stress on neural circuitry within the hippocampal formation is the suppression of neurogenesis by glucocorticoids. Stress-induced suppression of cell proliferation in the DG has been reported in several different mammalian species and there is considerable evidence arguing for a role for glucocorticoids as the mediators of the stress response. Elimination of circulating adrenal steroids by adrenalectomy, for example, increases cell proliferation and neurogenesis in the adult dentate gyrus (Cameron and McKay, 1999). Exogenous administration of corticosterone, on the other hand, suppresses proliferation (Cameron and Gould, 1994). Glucocorticoids have been shown to inhibit the proliferation and differentiation of neural progenitors, and also the survival of young neurons (Wong and Herbert, 2004, 2006). These effects are likely to be mediated directly through high affinity mineralocorticoid receptors (MR) and low affinity glucocorticoid receptors (GR) that are expressed at various stages of maturation and also indirectly through changes in network activity of the hippocampal formation (see chapter by Joels in this volume). Analysis of receptor distribution in the dentate gyrus of rodents reveals that GRs are expressed in both neural progenitors and mature dentate granule cells, while MRs are expressed only in the latter. Throughout most of adulthood, neither GRs nor MRs are expressed in immature neurons (Cameron et al., 1993; Garcia et al., 2004a). However, in aged rodents GR and MR expression is seen in immature neurons, suggesting that immature neurons at this stage, but not earlier in the animal's life, may show increased sensitivity to corticosterone action.

The dynamic expression of GR and MR during neurogenesis and the ability of corticosteroids to regulate the expression of growth factors such as IGF-1, BDNF and EGF (Islam et al., 1998; Schaaf et al., 2000), which have distinct effects on proliferation and survival (Kuhn et al., 1997; Aberg et al., 2000; Sairanen et al., 2005), illustrate the cell autonomous and non-cell autonomous ways by which corticosteroids can affect neurogenesis. It should be noted that the sensitivity of neurons or neural progenitors to corticosteroids must be studied with the state of the neuron or network in

mind. For example, glucocorticoids have deleterious effects on neurogenesis during stressful episodes but not during physical activity. This may be due to the fact that physical activity, unlike stress, elicits the production of growth factors that may buffer the effects of corticosteroids on neurons. Likewise, given the differences in the developing and adult brain, an increase in glucocorticoids during early postnatal life may have profoundly different effects from those in adulthood. A recent study modeling early life stress using a maternal separation paradigm in rodents supports this idea (Mirescu et al., 2004). Maternal separation during the early postnatal period in rodents leads to persistent changes in the HPA axis, protracted release of corticosterone in response to mild stressors, increased anxiety behavior (Huot et al., 2001), impaired maternal care (Lovic et al., 2001) and impaired spatial navigation (Huot et al., 2002). Rats subjected to prolonged maternal deprivation during the early postnatal period also showed reduced proliferation in the dentate gyrus of neural progenitors in adulthood. Interestingly, the early life stressor did not affect the number of mature neurons, suggesting a compensatory increase in survival of newly generated neurons. The authors in this study showed that the change in proliferation could be rescued in adulthood by adrenalectomy and by reducing corticosteroid production. Without adrenalectomy, the corticosterone levels were normal in stressed animals, not only under baseline conditions but also in response to a stressor, suggesting that the suppressed proliferation was likely to be result of increased sensitivity to corticosteroids rather than increased levels (Mirescu et al., 2004). It is tempting to speculate that a shift in the temporal pattern of MR and GR distribution during neurogenesis may contribute to this increased sensitivity.

It is possible that changes in neurogenesis as a result of HPA axis dysregulation contribute to the pathophysiology of MDD by affecting the role of the hippocampus in learning and other cognitive-emotional processes. Preclinical studies (discussed later) have proven tremendously informative in defining the physiological relevance of adult hippocampal neurogenesis to these processes, and have greatly facilitated our understanding of how

stress-mediated suppression of neurogenesis may be relevant to the pathophysiology of MDD. A second possible consequence of the stress-mediated suppression of neurogenesis is that the ability of the hippocampus to regulate HPA activity becomes compromised. However, evidence directly linking changes in dentate gyrus function with HPA activity is scarce. Lesions of the hippocampus and fimbria-fornix transections reduce the ability of dexamethasone to inhibit stress induced adrenocortical responses and results in hypersecretion of glucocorticoids and ACTH following stressful stimuli (Knigge, 1961; Sapolsky et al., 1989; Herman et al., 1992; Feldman and Weidenfeld, 1993; Bratt et al., 2001; Goursaud et al., 2006). **Antagonism of GR in the rat hippocampus results in hypersecretion of ACTH and corticosterone following stressful stimuli (Sapolsky, 1994; Feldman and Weidenfeld, 1999).** Analysis of subfields within the hippocampal formation confirms the differential contributions of CA fields and the dentate gyrus in the ventral hippocampus in regulating HPA reactivity. Intriguingly, lesion studies indicate that damage of ventral subiculum but not ventral CA1 or dentate gyrus results in prolonged glucocorticoid responses (Herman et al., 1992, 1995). **By contrast, electrical stimulation of DG in anesthetized animals inhibits corticosteroid secretion (Dunn and Orr, 1984).** These studies suggest that lesions of DG in adulthood may be compensated for by activity in structures downstream such as the subiculum. Genetic manipulations that specifically impair glucocorticoid signaling in the DG both in adulthood and in early postnatal life will prove critical in establishing the link between hippocampal neurogenesis and HPA reactivity.

In sum, the well-documented effects of stress on neurogenesis suggest that patients with MDD are likely to show reductions in neuronal proliferation. While it is plausible that a reduction in neurogenesis in turn contributes to HPA dysregulation, there is as yet no evidence for this.

### **Neurogenesis and antidepressants**

It is well recognized that all of the major classes of ADs are associated with a several week delay in

onset. This delay is likely to reflect changes in structural and synaptic plasticity in the brain mediated by multiple mechanisms involving monoaminergic signaling and neurotrophins. PET imaging studies on MDD patients treated with SSRIs such as paroxetine and fluoxetine have helped define a neuroanatomical basis comprising corticolimbic circuits (Seminowicz et al., 2004). Structures that showed changes in metabolic activity included the subgenual cingulate, hippocampus and prefrontal cortex (Mayberg et al., 2000; Kennedy et al., 2001). One form of structural plasticity within the hippocampus that is consistent with the delayed onset of ADs is the birth and subsequent integration of newborn dentate granule cells in the adult dentate gyrus. Moreover, almost all ADs known to date increase adult neurogenesis. Therefore, the idea that ADs may work through enhancing neurogenesis has received abundant attention and is now considered central to the neurogenic hypothesis of MDD (Malberg and Schechter, 2005).

### *Neurogenic effects of antidepressant treatments*

Numerous groups have shown that different classes of ADs including 5-HT and norepinephrine selective reuptake inhibitors, tricyclics, monoamine oxidase inhibitors, phosphodiesterase inhibitors and electroconvulsive shock therapy increase neurogenesis (Madsen et al., 2000; Malberg et al., 2000; Manev et al., 2001; Nakagawa et al., 2002b). AD treatment does not appear to affect the ratio of newly generated neurons to glial cells, with the majority of newborn cells adopting the neuronal fate. The neurogenic effects of ADs are specific to the SGZ, and are not observed in other components of the ventricular system such as the lateral ventricles or the subventricular zone. Moreover, administration of non-AD psychotropic drugs such as haloperidol does not increase hippocampal neurogenesis (Eisch, 2002). Other treatments reported to have AD effects, including exercise (Babyak et al., 2000; Singh et al., 2001; Motl et al., 2004), environmental enrichment and estrogen, have also been shown to increase neurogenesis (van Praag et al., 1999; Tanapat et al., 1999;

Rhodes et al., 2003; Meshi et al., 2006). In addition, also lithium, which is used in the treatment of bipolar disorder increases neurogenesis (Chen et al., 2000). The one AD treatment that has not been shown to enhance neurogenesis is repetitive transcranial magnetic stimulation or rTMS, which is still awaiting FDA approval (Loo and Mitchell, 2005). While rTMS has been shown to reverse the effects of chronic psychosocial stress on stress hormone levels, it does not upregulate neurogenesis (Czeh et al., 2002).

That ADs block the behavioral effects of stress and restore normal levels of neurogenesis in the adult hippocampus lends further credence to the possibility that ADs may work by increasing neurogenesis to exert their behavioral effects. In tree shrews, chronic exposure to psychosocial conflict results in a decrease in cell proliferation, which is blocked by treatment with the atypical AD tianeptine (Czeh et al., 2001). In another model of depression, the learned helplessness (LH) paradigm, exposure to inescapable shock engenders depressive behavior and a reduction in hippocampal cell proliferation, both of which, are reversed by AD treatment (Cryan et al., 2002; Malberg and Duman, 2003). In addition, ECS enhances cell proliferation after chronic corticosterone treatment (Hellsten et al., 2002).

It is well known that ADs have pleiotropic effects on neuronal circuits. That a diverse range of ADs appears to enhance neurogenesis indicates that the dentate gyrus may be a neuroanatomical substrate to target for the development of novel AD treatments. In the next section, we describe recent preclinical studies elucidating how SSRIs modulate adult hippocampal neurogenesis, and then in the following sections we describe work from animal models aimed at identifying whether neurogenesis is necessary for the behavioral effects of AD treatments.

### ***Serotonin-dependent ADs and hippocampal neurogenesis***

SSRIs represent the most successful class of ADs identified to date. Based on our understanding of neurogenesis in the SGZ, it is conceivable that

SSRIs act directly on progenitors or immature neurons to influence processes such as proliferation, differentiation, maturation and survival. In addition, SSRIs are also likely to modulate network activity within the dentate gyrus and as a result, regulate neurogenesis indirectly. By virtue of their effects on neurogenesis, SSRIs may be capable of driving replacement or turnover within the dentate gyrus and catalyzing the insertion of newly generated neurons with distinct electrophysiological and biochemical properties. The best-characterized effect of SSRIs to date is the increase in proliferation of neural progenitors in the SGZ. Studies in rodents indicate that a 14-day, but not shorter-term, administration of fluoxetine (1–5 days) is sufficient to upregulate cell proliferation (Malberg et al., 2000). By contrast, a longer treatment regimen is required to enhance survival of newly generated neuroblasts. Fluoxetine treatment for 28 days, but not 14 days, following BrdU injection resulted in an increase in cell survival (Malberg et al., 2000; Nakagawa et al., 2002a).

The delay with which the neurogenic effects emerge after the initiation of SSRI treatment provides a potential mechanism to explain the therapeutic lag in the effects of these drugs. Namely, it could be that the therapeutic effects depend on the increase in proliferation, which itself requires several weeks of treatment. However, closer inspection of this hypothesis reveals several shortcomings. It is unlikely that a boost in proliferation would produce an immediate psychological effect. Rodent studies indicate that newborn neurons do not become functionally integrated until approximately 2–4 weeks after exiting the cell cycle, so it would seem that any functional effects elicited by the increase in proliferation would not appear until that time (Esposito et al., 2005). This means that behavioral effects of SSRIs mediated by increased proliferation should not manifest until about 4 weeks after treatment initiation. In contrast, some behavioral effects of AD drugs in animal models begin immediately following acute treatment, and virtually all the behavioral effects manifest within 4 weeks of SSRI treatment. In primates the time required for maturation of new neurons is greater than in rodents (Kohler et al.,

2006), so the predicted therapeutic lag would be even longer. A recent meta-analysis of clinical data indicates that some of the therapeutic effects of SSRIs may commence very rapidly after treatment initiation (within 1–2 weeks) (Taylor et al., 2006). Thus, increases in proliferation are unlikely to underlie the early onset effects of these drugs, but it remains plausible that neurogenesis contributes to the more long-term effects.

Consistent with this interpretation, remarkable preliminary data from Meltzer, Deisseroth and colleagues suggest that mature adult-born neurons contribute to the behavioral effects of SSRIs (Meltzer et al., 2006). In this study, rats were given 7 days of fluoxetine treatment and then tested behaviorally 1 month later. At that time point, the previously treated rats showed enhanced performance in the forced swim test, and histology revealed an increase in the number of newly generated neurons. The results suggest that the proliferative effects of SSRIs may appear sooner than once thought (after 1 week rather than 2 weeks of treatment), and that some behavioral effects of these drugs depend not on the acute presence of the drug but rather on slow, time-dependent processes initiated by drug treatment, such as neurogenesis and circuit reorganization.

The studies that examined the effects of fluoxetine on proliferation do not identify the specific types of neural progenitors that respond to changes in 5-HT levels. A recent study addressed this question using transgenic mice in which expression of a fluorescent reporter gene was regulated by a nestin promoter fragment. Because nestin is expressed in multiple progenitor cell types, this approach allowed the visualization and quantification of the distinct sub types of neural progenitors that reside within the SGZ (Encinas et al., 2006). The results of this study showed that only a specific proliferative cell type, the transiently amplifying neural progenitor (ANP) that exists as an intermediate between the type I radial glial-like neural progenitor and the type II cell (Filippov et al., 2003; Tozuka et al., 2005; Encinas et al., 2006), directly responds to fluoxetine. Moreover, the study confirmed that once exposure to fluoxetine ends, the rate of progenitor cell division is restored to baseline and that

the increase in ANPs translates into a net increase in the number of new neurons.

A net increase in the number of mature neurons implies that SSRIs also increases the population of immature neurons. It is presently not clear how SSRIs influence the maturation of immature neurons with regards to their physiological properties, synaptic connectivity and dendritic complexity. What is well appreciated, however, is that SSRI treatment results in the induction of growth factors and neurotrophins whose effects on maturation and survival are well understood (Carlezon et al., 2005; Duman and Monteggia, 2006) and, importantly, whose receptors are expressed in immature neurons. It is also possible that SSRIs may induce the secretion of growth factors from neural progenitors, which then influence the function of neighboring mature granule cells in a paracrine manner. There is no evidence for this as yet.

The consequences of increased proliferation and survival of newly generated cells following fluoxetine treatment for the net size of the granule cell population of the dentate gyrus have not been ascertained. One study suggested that there may not be a net change in the size of the dentate gyrus because the increase in newly generated neurons is offset by death of previously born mature granule cells (Sairanen et al., 2005). Based on their data showing that chronic fluoxetine treatment increases not only proliferation and survival of newly generated neurons but also the rate of apoptosis, the authors argue that the net size of the dentate gyrus does not change with chronic AD treatment.

Finally, it is plausible that SSRI treatment alters the physiological properties of newly generated neurons, generating a cohort of cells within the dentate that are unique. These unique cells may confer greater adaptive potential to the dentate gyrus than naïve newly generated neurons. Much work remains to be done in this area to address the different ways by which SSRIs influence neurogenesis.

Delineating the pattern of expression of distinct 5-HT receptor subtypes within different cell types in the SGZ and the DG will shed light on how changes in 5-HT can elicit the diverse range of effects discussed here. It follows that the



identification of genes downstream of 5-HT receptors that mediate the behavioral effects of ADs will pave the way for developing neurogenic non-monoamine based therapeutics. Preclinical studies have proven invaluable in defining the contribution of neurogenesis to the etiology and treatment of MDD as they allow for discernment between correlation and causality.

### **Preclinical studies: in the search for causality**

Ultimately, whether neurogenesis is causally related to the etiology or treatment of depression requires the use of animal models in which neurogenesis and emotional state can be experimentally manipulated. If reduced neurogenesis contributes to depression, it should be possible to produce a depressive phenotype by experimentally reducing neurogenesis. Conversely, behavioral manipulations that produce a depressive phenotype should reduce neurogenesis and do so before the behavioral manifestations of depression develop. Of course, the predictive value of such experiments will depend on the specificity of the methods for manipulating neurogenesis and the validity of the animal models of depression. This section will review recent work that addresses the role of neurogenesis in the etiology and treatment of MDD assessed in preclinical models.

### ***Lessons from stress based depression paradigms and neurogenesis***

One prediction drawn from the neurogenic hypothesis of MDD is that behavioral manipulations that produce depressed behavior in animals should produce a concomitant decrease in neurogenesis. Several methods have been used to produce depression-like behavior in rodents, all involving the exposure to inescapable stress. One such procedure is LH, originally developed by Seligman and colleagues (Overmier and Seligman, 1967; Seligman and Beagley, 1975). LH is a relatively short-term procedure in which animals are exposed to inescapable shock inside a conditioning chamber. Subjects are then given an escape/avoidance task in which shock is controllable (e.g., shuttling from

one side of the chamber to the other cancels or terminates the shock). Exposure to inescapable shock impairs subsequent acquisition of the escape/avoidance task (relative to naïve subjects), arguably because the animal has learned it is helpless (Willner and Mitchell, 2002). LH training also reduces cell proliferation in the DG. Treatment with AD drugs alleviates both the behavioral helplessness (Malberg and Duman, 2003; Chourbaji et al., 2005) and the reduction in cell proliferation (Malberg and Duman, 2003). However, there are several reasons why reductions in proliferation are not a likely mechanism of the behavioral helplessness. First, behavioral helplessness manifests immediately with exposure to inescapable shock, and it is unlikely that a reduction in proliferation could so rapidly give rise to a behavioral effect. If the reduction in proliferation were to impact behavior, the effects would more likely manifest 1–3 weeks after the onset of the reduction in proliferation, at the time when the newborn cells would be becoming functionally integrated into DG circuits. Similarly, acute dosing with AD drugs is sufficient to alleviate behavioral helplessness (Malberg and Duman, 2003; Chourbaji et al., 2005), but the neurogenic effect of these drugs requires chronic treatment (Malberg et al., 2000). Finally, a recent study has demonstrated that LH training in rats reduces cell proliferation in all subjects, but only a subset of subjects display behavioral helplessness (Vollmayr et al., 2003). One unexplored possibility invoked by these studies is that the extant population of immature neurons, rather than the proliferative pool, is a substrate for the depressogenic effects of stress. Studies are underway to test this hypothesis.

Neurogenesis can more plausibly be linked to the effects of chronic exposure to stress, which have been studied extensively in animals. This work typically involves exposing animals to variety of mild stressors over a period of several weeks. Stressors include food and water deprivation, temperature changes, restraint and tail suspension (Strekalova et al., 2004; Willner, 2005; Mineur et al., 2006). There are variations in the methods used for chronic stress in rats (Willner et al., 1987, 1992; Willner, 2005) and mice (Mineur et al., 2003, 2006; Strekalova et al., 2004). The effects of

chronic stress include a reduction in sucrose preference, which has been interpreted as anhedonia (Willner et al., 1987; Strelakova et al., 2004), alterations in sleep–wake cycle, reduced sexual and self-care behavior, and increases in anxiety-like behavior in traditional tests such as the elevated-plus maze (Willner, 2005). Unlike the effects of LH, the behavioral effects of chronic stress are ameliorated by chronic but not acute treatment with ADs (Willner et al., 1987; Yalcin et al., 2005), suggesting that chronic stress may be a better model of depression because it captures the therapeutic lag seen in human patients. An abundance of research demonstrates that hippocampal neurogenesis is reduced by a variety of chronic stress procedures (for review, see Duman, 2004), and this reduction in neurogenesis is blocked by chronic treatment with AD drugs (Alonso et al., 2004). Moreover, a recent study has shown that among rats exposed to chronic stress, only a subset respond behaviorally to SSRI treatment (Jayatissa et al., 2006). Interestingly, neurogenesis was restored to normal levels only in the behaviorally identified responders.

### ***Does blockade of neurogenesis produce symptoms of depression?***

The animal research on chronic stress evidences an intriguing correlation between the rate of neurogenesis and emotional state. Chronic stress produces a behavioral phenotype analogous to aspects of depression while reducing neurogenesis. AD drugs restore neurogenesis and ameliorate the behavioral phenotype. Does this correlation reflect that neurogenesis is a causal mechanism for these behavioral changes? Or is neurogenesis simply a marker for changes in other biological pathways or network activity?

We have begun to address this question experimentally by blocking hippocampal neurogenesis and then examining the behavioral consequences. One method of arresting neurogenesis is to subject the brain to low doses of X-irradiation. Irradiation kills mitotic cells such that neurogenesis is arrested virtually completely (Monje et al., 2002, 2003; Wojtowicz, 2006). In our laboratory, a shield is

used to target X-rays specifically over the hippocampus, while protecting regions anterior and posterior, including the subventricular zone. Blocking neurogenesis with this procedure has no effect in a number of relevant behavioral tasks, including the novelty-suppressed feeding test (Santarelli et al., 2003) and the novelty-induced hypophagia test (our unpublished data). Both of these tests are AD screens that measure the latency of a mouse to venture into the center of an open field or novel context to obtain food. Latency-to-feed is decreased by chronic AD drug treatment and acute anxiolytic treatment, but not by acute AD drug treatment (Bodnoff et al., 1989; Dulawa et al., 2004). Irradiation does not affect behavior in two traditional anxiety tests, the elevated-plus maze and light-dark choice test (our unpublished data), nor does it increase the susceptibility of mice to the effects of chronic stress (Santarelli et al., 2003).

We have also examined some of these behaviors in a transgenic mouse line in which neuronal proliferation can be blocked conditionally. The mouse line expresses herpes-simplex virus thymidine kinase (HSV-TK) under control of the GFAP promoter (GFAP-TK) (Garcia et al., 2004b). Mitotic cells expressing HSV-TK are killed by the antiviral drug ganciclovir. Thus, in this mouse, the dividing neuronal progenitors, which express GFAP, are killed after ganciclovir is administered, and as a result, neurogenesis is reduced to low levels (Garcia et al., 2004b; Saxe et al., 2006). As with irradiation, blocking neurogenesis in this mouse line had no effect on anxiety-like behavior in several tests, including the open field, NSF test, or light-dark choice test (Saxe et al., 2006). Thus, we have not found any evidence that blocking neurogenesis in adult mice produces a depression-like phenotype.

### ***A role for hippocampal neurogenesis in learning***

The only domain in which direct behavioral effects of arresting neurogenesis have been reported is in learning and memory. Indeed, the very first evidence for a behavioral function of neurogenesis in mammals came from studies of learning and

memory. These studies showed that participating in a hippocampus-dependent classical conditioning procedure (trace eyeblink conditioning) enhances the survival of newborn neurons in the SGZ (Gould et al., 1999a) and that reducing neurogenesis with the anti-mitotic compound methylazoxymethanol acetate (MAM) impairs acquisition of the same task (Shors et al., 2001). The use of MAM is encumbered by deleterious side effects and moreover, it does not completely block neurogenesis (Dupret et al., 2005). Subsequent experiments using more targeted methods for arresting neurogenesis have confirmed that neurogenesis is required for some hippocampus-dependent learning tasks (Snyder et al., 2005; Saxe et al., 2006; Winocur et al., 2006). A recent study from our laboratory has also revealed a paradoxical role for hippocampal neurogenesis in a hippocampus-dependent working memory paradigm, where ablation of newly generated neurons results in improved performance (Saxe et al., 2007).

Perhaps the most compelling of these findings is the requirement of neurogenesis for contextual fear conditioning, which has been demonstrated in two species (rats and mice) using two different methods for arresting neurogenesis (Saxe et al., 2006; Winocur et al., 2006). Contextual fear conditioning is a form of Pavlovian conditioning produced by pairing a distinctive context (spatial location) with footshock. As a result of the pairing, animals exhibit characteristic fear responses (e.g., freezing, defecation, potentiation of the startle response) when re-exposed to the context. Lesions to the hippocampus often impair this form of learning (Phillips and LeDoux, 1992; Matus-Amat et al., 2004), presumably because the hippocampus participates in mnemonic encoding of the spatial context. Blocking neurogenesis prior to training in this procedure reduces the amount of the contextual fear expressed when rodents are re-exposed to the training context. Importantly, blocking neurogenesis does not impair fear conditioning to a discrete tone stimulus, indicating that shock sensitivity and motor control of the fear response are not impaired. The impairment of contextual fear conditioning may thus reflect a

requirement of neurogenesis for the encoding of novel contexts and/or for assigning emotional valence to contexts.

How (and whether) these learning impairments relate to depression is unclear. Cognitive impairments have been reported in depression, but cognitive impairment is not a cardinal feature of the disease, in contrast to some other psychiatric illnesses, namely schizophrenia. Still, it is certainly the case that depressed patients have an impaired ability to “contextualize” negative emotions, in that these emotions are overgeneralized across experiences and situations. Much more research into the putative role of neurogenesis in contextual learning will be needed to determine whether reduced neurogenesis could give rise to these features of depression.

#### *Neurogenesis is required for some behavioral effects of AD drugs*

Although animal models have not provided evidence that reduced neurogenesis causes depression-like symptoms, these models have produced evidence that neurogenesis is involved in the therapeutic effects of AD drugs. Three recent studies have used the targeted irradiation procedure described above to test whether DG neurogenesis is required for the behavioral effects of AD drugs in rodent models. A study conducted in our laboratory demonstrated that neurogenesis is required for the effects of both imipramine, a classic tricyclic AD, and fluoxetine in two mouse behavioral screens for AD activity (Santarelli et al., 2003), the NSF test and a chronic stress procedure. Importantly, this study has been replicated in our laboratory using the GFAP-TK mice (unpublished results). In a separate series of experiments conducted by another laboratory, the synthetic cannabinoid HU210 was shown to have AD-like effects in the NSF paradigm following 10 days of treatment, and, interestingly, this effect was blocked by X-ray irradiation (Jiang et al., 2005). In addition, there is a recent preliminary report using rats (Meltzer et al., 2006) that irradiation blocks the behavioral effects of fluoxetine in the

forced swim test. Thus, a neurogenic dependence for the behavioral effects of ADs has been revealed for three different drugs in three different AD screens and using two different ways to ablate neurogenesis.

The above work suggests that neurogenesis may be a critical substrate for AD efficacy. However, an important limitation of this work is the reliance on a very limited number of animal models and AD treatments. It is unlikely that the three behavioral assays used in these experiments capture all the clinically relevant features of AD treatments, and consequently it remains possible that some clinically important features of these treatments are neurogenesis-independent. Indeed, two more recent studies from our lab confirm that this caveat is valid.

One study from our laboratory (Holick et al., 2007) examined the effects of AD drugs on behavior and DG neurogenesis in the Balb-c mouse strain, a strain that exhibits high anxiety in behavioral tests. In this strain, chronic fluoxetine treatment reduced anxiety-like and depressive behavior in the novelty-induced hypophagia and forced-swim paradigms but failed to increase neuronal proliferation. Not surprisingly, the behavioral effects of these drugs are not blocked by irradiation in this strain. A second study found that the anxiolytic effects of environmental enrichment do not require neurogenesis (Meshi et al., 2006).

In sum, these studies suggest that AD-like effects can be achieved through at least two different pathways, one that is neurogenesis-dependent and one that is neurogenesis-independent. AD drugs and cannabinoids appear to use a neurogenesis-dependent pathway in some circumstances but not in others; chronic stress may be one factor that governs this dichotomy. Enrichment appears to use a neurogenesis-independent pathway either alone or in combination with the neurogenesis-dependent pathway. An important outstanding question not addressed by these experiments is whether the upregulation of neurogenesis is *sufficient* to produce AD effects. Testing this hypothesis will require new methods for very specifically upregulating aspects of neurogenesis.

## Summary

*General insights: is neurogenesis a missing link or is the link still missing?*

Research on MDD in the last decade has led to considerable maturation of our understanding of how different neural circuits function in a normal brain and in the context of pathology. Several notable findings have emerged from studies in humans with MDD and preclinical models of MDD. First, the AD response and the pathogenesis of MDD may have different neural substrates. Second, the pathogenic mechanisms may differ from those that underlie the pathophysiology of MDD. Third, any model explaining the etiology of MDD must incorporate genetic vulnerability, stressors, critical periods and multiple neural circuits. In other words, MDD is more likely than not, a result of multiple “hits” to the brain (deficits in multiple neural substrates). This last finding underscores the need for more refined preclinical models for depression. In this section, we revisit the neurogenic hypothesis of MDD with attention to the evidence discussed thus far in the context of etiology, pathophysiology and treatment.

### *The neurogenic hypothesis and the etiology of MDD*

Only recently the neurogenic hypothesis of MDD joined the neurotrophic and network hypotheses as a candidate to explain the neurobiological basis of MDD.

Unlike the neurotrophic and network hypothesis, however, the neurogenic hypothesis implicates only one brain region, the dentate gyrus, as the primary neural substrate for the etiology of MDD and the AD response.

As this review makes clear, the evidence for neurogenesis as an etiological factor in MDD is scarce at best. Pathological analyses of postmortem tissue obtained from patients with MDD have not revealed alterations in the size of the dentate gyrus, decreased number of proliferative cells, or changes in the degree of ongoing apoptosis. The data on apoptosis do not indicate the age of neurons that

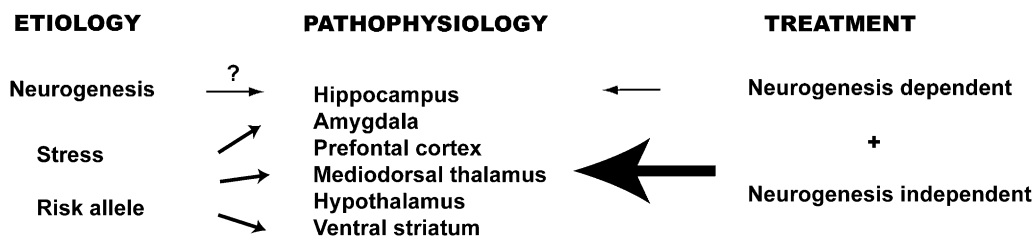


Fig. 2. A model to evaluate the role of neurogenesis as a substrate in the etiology, pathophysiology and treatment of MDD. MDD is likely to arise from the synergistic effects of stress, biological vulnerability conferred by risk alleles and deficits in multiple neural circuits. Whether hippocampal neurogenesis is involved in the etiology of MDD is at present unclear. Altered hippocampal neurogenesis may result as a consequence of pathogenic mechanisms and contribute to the pathophysiology of MDD. The treatment of some, but not all, symptoms of MDD may rely on neurogenesis.

are dying and therefore, preclude an assessment of changes in rates of turnover or survival. As noted earlier in this chapter, more studies on postmortem tissue obtained from non-medicated patients are required to conclusively characterize dentate gyrus neurogenesis in depressed individuals. Nevertheless, these data establish that changes in hippocampal volume are unlikely to result from changes in hippocampal neurogenesis. Preclinical studies have yielded data more directly controverting the role of neurogenesis in the etiology of MDD: ablation of neurogenesis in adult otherwise normal animals does not engender a depression-like phenotype. However, there are some important caveats to these preclinical studies. It is almost certainly the case that MDD involves the simultaneous presence of multiple risk factors or “hits” (Fig. 2). If this were the case, ablation of neurogenesis in wild-type adult animals would not be sufficient to elicit a depression-like phenotype. The ablation of neurogenesis might create a diathesis for depression that would only be revealed in the presence of other genetic or environmental insults. Moreover, the timing with respect to when the brain experiences an insult, whether it be genetic or environmental, is also critical. Clearly, more studies are needed that incorporate the effects of stressors and assess the consequences of altering neurogenesis during the early postnatal period in rodents with genetic backgrounds that harbor different risk alleles. These studies will reveal whether changes in neurogenesis lend a diathesis for MDD, and inform us about the complex interplay between multiple neural circuits in

directing the emotional trajectory. Finally, longitudinal neuroimaging studies in humans are needed to reveal how the hippocampal landscape changes with the appearance of the first symptoms of MDD and over time.

#### *The neurogenic hypothesis and the pathophysiology of MDD*

The increasingly appreciated role for neurogenesis in hippocampus-dependent learning as defined by work from several different laboratories using rodents provides evidence that neurogenesis makes a functionally significant contribution to hippocampal circuits. It is thus plausible that the putative reductions in neurogenesis associated with MDD have important psychological implications. These could include cognitive deficits, which are a possible mechanism of the emotional symptoms of the disease (Beck, 2005). In addition, it is now appreciated that the hippocampus, particularly its ventral (anterior, in humans) extent, has a central role in emotional regulation. The development of higher resolution neuroimaging techniques will enable us to visualize changes in dentate gyrus activity in patients with MDD and during learning. The use of novel genetic approaches to selectively manipulate the maturation of newborn neurons influence their survival, and drive turnover of mature dentate granule cells will undoubtedly enhance our understanding of how neurogenesis contributes to dentate function and to the deficits seen in MDD.



### *The neurogenic hypothesis and the treatment of MDD*

The finding that neurogenesis is one mechanism used by ADs to exert their behavioral effects has now been repeated by several different laboratories using rodents. This is in striking contrast to the absence of data implicating neurogenesis in the pathogenesis of MDD. One interpretation of this apparent paradox (besides the limitations of current preclinical models highlighted in section “The neurogenic hypothesis and the etiology of MDD”) is that the etiology and treatment of MDD may have different neural substrates. Such a dissociation is suggested by a recent association study that looked at 21 candidate polymorphisms and showed that the genetic basis for the capacity to respond to monoamine-based ADs differed from that of susceptibility to MDD (Garriock et al., 2006). An interesting parallel was demonstrated by preclinical studies on BDNF and depression, which showed that increased BDNF signaling in the hippocampus is sufficient to induce AD-like effects, but genetic ablation of BDNF on its own does not elicit a depression-like phenotype (Duman and Monteggia, 2006). While the data from preclinical studies and ADs are encouraging, more work is needed to solidify the requirement for neurogenesis in mediating the behavioral effects of ADs. Conspicuously absent from the roster of experiments are those that show that increased neurogenesis is *sufficient* for the behavioral effects of ADs. Experiments along these lines using genetic approaches to specifically increase the number of newly generated neurons are currently underway in our laboratory. Moreover, given the pleiotropic effects of ADs on neurogenesis, it at present unclear whether immature neurons or the adult-generated mature dentate granule cells are required to induce behavioral change. Inducible genetic approaches using promoters specific to these different cell types will allow for cell type specific manipulations to unequivocally identify the cellular substrates and mechanisms underlying the neurogenic-dependent AD response.

In interpreting the data on the neurogenic dependence of ADs, we must remind ourselves of the

potentially different ways by which ADs may rely on neurogenesis for their behavioral effects (Fig. 1, Drew and Hen, in press). It is plausible that the short-term effects of ADs, for example, are mediated by ADs acting on the extant reservoir of adult-generated immature neurons or by accelerating the maturation process of an extant population of adult-generated immature neurons with concomitant replacement/addition to the dentate gyrus. Likewise, the rapid effects of ADs in reversing behavioral changes induced by stress in paradigms such as LH discussed earlier could also be mediated through the extant population of immature neurons or through adult-generated mature dentate granule cells. In this regard, it is worthy to note that inducing BDNF and CREB expression in the DG but not other hippocampal subfields (or other brain regions) is sufficient to elicit an AD response (Chen et al., 2001; Shirayama et al., 2002; Duman and Monteggia, 2006). Thus, the DG is an attractive neural substrate for the AD response and these studies highlight a previously unrecognized function for the dentate gyrus. Given our present understanding of DG function (see chapter by Kesner in this volume), it is unclear how enhancement in processes such as pattern separation and conjunctive encoding contribute to AD-like behavior assessed in these depression paradigms. Whether cognitive behavior therapy, an endorsed line of treatment often used in parallel with AD drugs, increases activity in the DG is yet to be determined.

In conclusion, there is much work to be done on hippocampal neurogenesis to ascertain its role in the brain and still much more to establish a role for it in MDD.

The convergence of insights from preclinical studies and neuroimaging studies and identification of novel genetic risk alleles will undoubtedly help establish whether the neurogenic hypothesis can explain facets of this complex and debilitating psychiatric disorder. At the very least, the neurogenic hypothesis, like any elegant hypothesis, has succeeded in generating the momentum needed to rigorously test its tenets.

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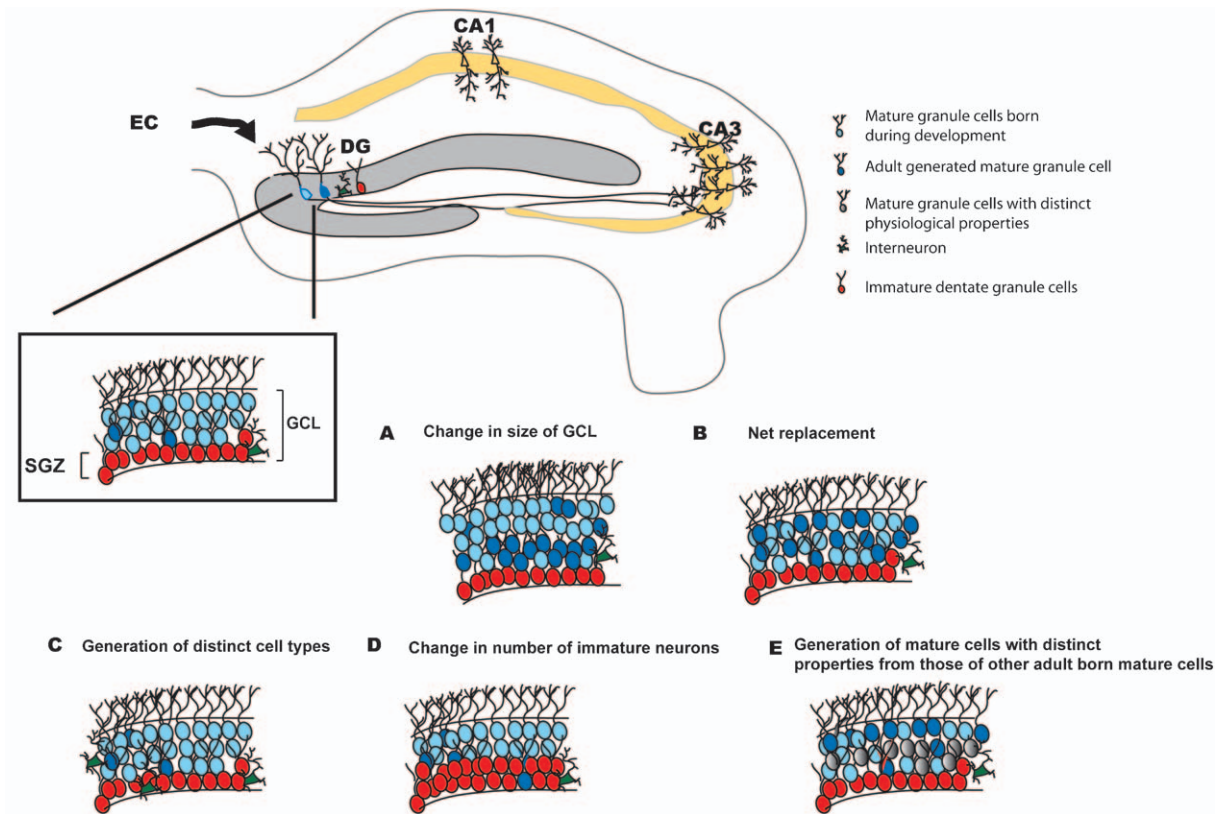


Plate 38.1. A schematic of the dentate gyrus granule cell layer (GCL) illustrating the different ways by which neurogenesis can influence its structure and function. Boxed panel reveals a cross section of the dentate GCL with the different populations that reside within it: mature granule cells born during development (light blue), adult-generated mature granule cells (dark blue), adult-born immature neurons (red) and interneurons (green). Over the lifespan, the GCL may increase in size due to a net addition of new neurons (A) or may remain unchanged due to a net replacement of developmentally generated granule cells (B). Changes in neurogenesis can result in increased representation of interneurons (C), a larger pool of adult generated immature neurons (D) or the generation of mature neurons with distinct physiological and biochemical properties (E). Conceivably, neurogenesis may be altered in any one of these ways in MDD. Conversely, AD drugs may influence DG function in more than one way to exert their behavioral effects. (For B/W version, see page 700 in the volume.)