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Neurogenesis and affective disorders

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Abstract

The neurogenesis hypothesis of depression was originally formed upon the demonstration that stress impacts levels of adult neurogenesis in the hippocampus. Since then much work has established that newborn neurons in the dentate gyrus are required for mediating some of the beneficial effects of antidepressant treatment. Recent studies combining behavioral, molecular and electrophysiological approaches have attempted to make sense of the role young neurons play in modulating mood by demonstrating a potential role in regulating the circuitry in the brain that underlies depression. Here we discuss the work that led to the neurogenesis hypothesis of depression, and the subsequent studies that have sought to test this hypothesis. We also discuss different animal models of depression that have been used to test the role of neurogenesis in mediating the antidepressant response.

Introduction

Elucidating the neurobiological basis of depression and determination of improved treatments is one of the foremost challenges for modern psychiatry. Mood disorders impact 7% of the world's population, and severe forms of depression affect 2–5% of the US population (Murray & Lopez, 1996). The heterogeneous nature of depression, which includes a multitude of diverse signs and symptoms, suggests a dysfunction of multiple distinct brain regions. Consistent with this idea, human imaging and *post mortem* studies have implicated areas including the prefrontal and cingulate cortex, hippocampus, striatum, amygdala and thalamus (Drevets, 2001; Liotti & Mayberg, 2001; Nestler *et al.*, 2002). Together, these brain regions operate a series of highly interacting circuits involved in depression (Manji *et al.*, 2001; Nestler *et al.*, 2002). The development of improved treatments will rely on identification of cellular mechanisms within these brain regions.

Over the last decade, it has become accepted that new neurons are produced throughout life in mammals in two discrete locations, the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus (Ming & Song, 2005). The neurons born in the SVZ migrate through the rostral migratory stream into the olfactory bulb and become interneurons, while those born in the SGZ migrate into the granular layer of the DG and eventually become mature granule neurons. The process of adult neurogenesis involves several steps, including the proliferation and fate specification of neural progenitors, neuronal migration, neuronal maturation and synaptic integration of the young neurons into the existing neuronal circuitry (reviewed throughout this issue). Various well-established histological markers can be used to mark or identify the cells at distinct points during this process, and the electrophysiological membrane properties of cells throughout the steps are well understood (Ming & Song, 2005; Suh *et al.*, 2009).

Much work has now suggested an important role for the hippocampus in the etiology of depression and mediation of the antidepressant response. Specifically, adult neurogenesis in the DG has gained considerable traction as a cellular substrate underlying the treatment of depression. The neurogenesis hypothesis of depression postulated that a decrease in the production of newborn granule cells in the DG is related to the pathophysiology of depression, while enhanced hippocampal neurogenesis is required for the beneficial effects of antidepressant treatment. Current evidence suggests that this hypothesis is at least partially true. While decreasing neurogenesis alone is not sufficient to drive a depression-like phenotype, there is a requirement for adult neurogenesis in mediating some of the beneficial effects of antidepressants.

Stress, antidepressants and the hippocampus

Several classic studies provided a foundation for the idea that the hippocampus is involved in the regulation of mood by demonstrating the vulnerability of the hippocampus to various hormones induced by stressful experiences (McEwen, 1999). In the CA3 subfield of the hippocampus, for example, 21 days of restraint stress or corticosterone treatment leads to atrophy of apical dendrites (McEwen *et al.*, 1995; McEwen, 1999). Adrenalectomy of an adult rat causes increased death of mature granule neurons in the DG (Sloviter *et al.*, 1989; Gould *et al.*, 1990). As for adult DG neurogenesis, there is also much evidence for regulation by stress (Dranovsky & Hen, 2006). Exposure to different forms of chronic stress, including social subordination, immobilization, physical restraint and footshock can suppress adult

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neurogenesis in multiple species (Gould *et al.*, 1997, 1998; Czéh *et al.*, 2001, 2002). The most likely mechanism by which stress suppresses adult neurogenesis in the hippocampus is via activation of the hypothalamic–pituitary–adrenal (HPA) axis and subsequent elevation of cortisol (glucocorticoid) levels. Several lines of evidence support this hypothesis. First, adrenalectomy increases adult DG neurogenesis (Cameron & Gould, 1994). Second, both acute and chronic treatment with corticosterone leads to a decrease in neurogenesis (Gould *et al.*, 1992; Cameron & Gould, 1994; Cameron *et al.*, 1998; Karishma & Herbert, 2002; Murray *et al.*, 2008; David *et al.*, 2009). Third, glucocorticoids also inhibit the proliferation and differentiation of neural progenitors and the survival of young neurons (Wong & Herbert, 2004).

From these results demonstrating effects of stress on adult neurogenesis in the DG arose the question whether antidepressant treatment could possibly reverse or mitigate these effects (Duman *et al.*, 1999). In other words, would antidepressant treatment result in a change in adult DG neurogenesis? Treatment of depression with selective serotonin reuptake inhibitors (SSRIs), the most common class of antidepressants, changes metabolic activity of the subgenual cingulate cortex, hippocampus and prefrontal cortex (Mayberg *et al.*, 2000; Kennedy *et al.*, 2001; Seminowicz *et al.*, 2004). SSRI treatment is associated with a delayed onset of therapeutic efficacy that has long been thought to reflect the temporal profile of desensitization of specific serotonin autoreceptors (Gardier *et al.*, 1996; Blier *et al.*, 1998; Slattery *et al.*, 2004). However, recent work has demonstrated that serotonergic tone prior to the onset of treatment is likely more important for governing this delay than autoreceptor desensitization (Richardson-Jones *et al.*, 2010). Another alternative to the autoreceptor desensitization hypothesis, which is not mutually exclusive, suggested that structural changes in neural circuitry, such as adult neurogenesis, also underlie this delay (Duman *et al.*, 1999; Duman & Monteggia, 2006; Sahay & Hen, 2007).

In line with this hypothesis, chronic antidepressant treatment increases adult DG neurogenesis as measured by uptake of bromodeoxyuridine (BrdU) in the SGZ (Malberg *et al.*, 2000; Manev *et al.*, 2001; Santarelli *et al.*, 2003; Duman, 2004; Perera *et al.*, 2007). Importantly, this increase is seen only in the SGZ and not in the SVZ, suggesting a specificity of the antidepressants to regulate hippocampal neurogenesis. This result holds true for multiple classes of antidepressants, including SSRIs, monoamine oxidase inhibitors, tricyclics (TCAs) and norepinephrine reuptake inhibitors (Malberg *et al.*, 2000; Santarelli *et al.*, 2003). Critically important, the proneurogenic effects of antidepressants are only seen with chronic, and not with acute, treatment, mirroring the time course for therapeutic action of these classes of antidepressants in humans (Malberg *et al.*, 2000). Further work has demonstrated that the effects of antidepressants on neurogenesis occur at multiple stages. In addition to increasing proliferation in the adult DG, chronic fluoxetine accelerates the maturation of young neurons by increasing dendritic arborization (Wang *et al.*, 2008). Furthermore, chronic fluoxetine decreases the number of newborn neurons expressing immature markers and yields a corresponding increase in those expressing mature markers (Wang *et al.*, 2008). In addition to antidepressant drugs, acute electroconvulsive seizure (ECS) is also effective at increasing neurogenesis (Madsen *et al.*, 2000; Malberg *et al.*, 2000; Manev *et al.*, 2001), as are environmental interventions that confer antidepressant-like behavior such as running, exercise and environmental enrichment (van Praag *et al.*, 1999; Babyak *et al.*, 2000; Singh *et al.*, 2001; Rhodes *et al.*, 2003; Van Praag *et al.*, 2005). Moreover, administration of psychotropic drugs without antidepressant activity does not increase neurogenesis (Eisch, 2002). Finally, as postulated, administration of various antidepressants can reverse the effect of stress on neurogenesis (Malberg & Duman, 2003; Dranovsky & Hen, 2006; Surget *et al.*, 2008). Most of these studies have used animal models, and in humans evidence remains somewhat limited regarding adult neurogenesis and psychiatric disorders. Recent work has suggested that exercise may induce neurogenesis using magnetic resonance imaging measurements of cerebral blood volume (CBV; Pereira *et al.*, 2007). In addition to CBV, magnetic resonance spectroscopy (MRS) has been successfully used to identify neural progenitors in live human brains (Manganas *et al.*, 2007). Furthermore, *post mortem* studies have shown that antidepressants increase neural progenitor cells in the human hippocampus (Boldrini *et al.*, 2009). Taken together, these results hint at an important role for adult neurogenesis in mediating the antidepressant response. However, these results are somewhat correlative, as it remained unclear whether this antidepressant-induced increase in neurogenesis is required for mediating the behavioral effects of antidepressant treatment.

Requirement for neurogenesis in mediating the antidepressant response

The next set of critical experiments sought to ablate adult neurogenesis in the DG and then test if the subjects were still responsive to antidepressants. The first attempt to address this problem used a simple but powerful method to destroy the niche of dividing cells: focal X-irradiation of the hippocampus (Santarelli *et al.*, 2003). Low doses of X-rays to the hippocampus while sparing the rest of the body and most of the brain with a lead shield resulted in a persistent > 85% reduction in BrdU incorporation into the SGZ. To test the importance of adult DG neurogenesis in the antidepressant response, irradiated and sham-irradiated mice were treated chronically with antidepressants (either the SSRI fluoxetine or the TCA imipramine) and subjected to behavioral testing. Sham-irradiated mice chronically treated with antidepressants display a decreased latency to enter the center and take a bite of a food pellet in the novelty suppressed feeding (NSF) test. Critically, mice that have been exposed to focal X-irradiation of the hippocampus, resulting in a loss of adult hippocampal neurogenesis, do not show this response to either fluoxetine or imipramine (Santarelli *et al.*, 2003). Further controls demonstrated that mice exposed to X-irradiation of the SVZ or cerebellum responded normally to the antidepressants. The results in the NSF test are of particular significance as mice only show responsiveness to antidepressants in this test after chronic treatment (Wang *et al.*, 2008), unlike other tests such as the forced swim or tail suspension where acute treatment is sufficient. These results suggested a necessary role for adult DG neurogenesis in mediating the antidepressant response.

These initial findings have now been confirmed by other studies (Surget *et al.*, 2008; Wang *et al.*, 2008; David *et al.*, 2009). Furthermore, in rats, the antidepressant effects of the synthetic cannabinoid HU210 in the NSF test and the effects of fluoxetine in the forced swim test are dependent on adult neurogenesis (Jiang *et al.*, 2005; Airan *et al.*, 2007). In addition, several depression- and anxiety-related behavioral effects induced by chronic mild stress, psychosocial stress or chronic corticosterone treatment are reversed by chronic antidepressant treatment in a neurogenesis-dependent manner (Surget *et al.*, 2008; David *et al.*, 2009; Schloesser *et al.*, 2010).

In addition to focal radiological approaches, genetic approaches have also demonstrated a requirement for neurogenesis in mediating the response to antidepressants (Li *et al.*, 2008). In this study, conditional ablation of TrkB, the high-affinity receptor for brain-derived neurotrophic factor (BDNF), was achieved in hippocampal neural progenitor cells (both early postnatal and adult) via usage of

either the hGFAP or Nestin promoter. These mice displayed significantly decreased proliferation in the DG, and were resistant to chronic antidepressant-induced proliferation and neurogenesis. Furthermore, these mice were insensitive to chronic antidepressant behavioral effects in the NSF and tail suspension tests. Control mice in which TrkB was ablated from mature neurons using a Synapsin promoter displayed wild-type levels of neurogenesis that could be increased with chronic antidepressant treatment, and were also responsive to antidepressant treatment behaviorally (Li *et al.*, 2008). Thus, a genetic manipulation that decreases neurogenesis also demonstrates a requirement in mediating the antidepressant response.

Potential mechanisms underlying antidepressant-induced neurogenesis

How might antidepressants induce neurogenesis? Perhaps the most prominent hypothesis involves the role of neurotrophic factors in the DG (Duman & Monteggia, 2006). More specifically, the neurotrophic hypothesis of depression states that decreased levels of neurotrophic factors such as BDNF could contribute to hippocampal atrophy seen in depressed patients, while the neurotrophic actions of antidepressants could underlie their beneficial therapeutic effects (Duman & Monteggia, 2006). This idea is supported by studies showing volumetric decreases in the hippocampus of depressed patients (Sheline *et al.*, 2003). In addition there were lower levels of BDNF in *post mortem* hippocampus of depressed patients, but higher levels in patients taking antidepressants at the time of death (Sheline *et al.*, 2003). A recent meta-analysis also demonstrated that serum levels of BDNF are lower in depressed than non-depressed subjects and, similarly, higher in patients following antidepressant treatment (Sen *et al.*, 2008).

In animal studies, direct infusion of BDNF into the DG exerts antidepressant effects (Siuciak *et al.*, 1997; Shirayama *et al.*, 2002; Kozisek *et al.*, 2008). Chronic antidepressant treatments using multiple classes of antidepressants, as well as acute ECS, exercise and transcranial magnetic stimulation all yield an increase in hippocampal BDNF levels (Nibuya *et al.*, 1995; Duman & Monteggia, 2006). Furthermore, numerous studies have together shown that multiple different stress paradigms decrease the expression of BDNF in the hippocampus (Duman & Monteggia, 2006).

Genetic approaches to manipulate BDNF/TrkB signaling for studies of depression and antidepressant treatment have yielded mixed results. Due to early postnatal lethality of BDNF-deficient mice, most work has used BDNF heterozygous (+/−) mice. BDNF +/− mice do exhibit an increased depression-like behavior in a learned helplessness task, but they also exhibit reduced pain sensitivity and no differences in tests of locomotor activity, exploration, hedonic sensitivity and behavioral despair (MacQueen *et al.*, 2001; Saarelainen *et al.*, 2003; Chourbaji *et al.*, 2004). One of these studies reports that the effects of antidepressant treatment are blocked in the BDNF +/− mice (Saarelainen *et al.*, 2003). Mice with a single nucleotide polymorphism (G196A; Val 66 to Met 66) in the BDNF gene that has implications for depression and anxiety disorders in humans also display increased anxiety behavior in the open field and elevated plus maze (Chen *et al.*, 2006). Mice using conditional ablation strategies have also yielded somewhat mixed results. In one study with conditional forebrain deletion of BDNF, mice have normal baseline depressive-like behavior, but the effects of antidepressant treatment in the forced swim test are attenuated (Monteggia *et al.*, 2004). Another study showed that conditional BDNF deficiency in the forebrain yields a depression-like behavior in the tail suspension test, but an antidepressant-like effect in the forced swim test (Chan *et al.*, 2006).

The link between neurotrophic signaling and adult neurogenesis is strong (Duman & Monteggia, 2006). As mentioned above, conditional deletion of TrkB in hippocampal neural progenitor cells yields decreased proliferation and resistance to antidepressant treatment (Li *et al.*, 2008). Chronic BDNF infusion into the hippocampus yields seizures, but is capable of increasing neurogenesis (Madsen *et al.*, 2000). One study also reports decreased basal proliferation in BDNF +/− mice (Lee *et al.*, 2002), while another demonstrates an effect specifically on survival of adult-born neurons (Sairanen *et al.*, 2005). Therefore, BDNF/TrkB signaling is likely important for both proliferation and circuit integration of adult-born hippocampal neurons. There is evidence demonstrating the importance of BDNF/TrkB-mediated increases in proliferation in mediating the antidepressant response (Li *et al.*, 2008), but the importance of the effects of BDNF on maturation and circuit integration of adult-born neurons remains unclear.

In addition to BDNF, there is also evidence for another neurotrophic factor, vascular endothelial growth factor (VEGF), in mediating the effects of antidepressants on adult neurogenesis. Similar to BDNF, multiple classes of antidepressants increase VEGF levels (Warner-Schmidt & Duman, 2007). Furthermore, potent inhibitors of the VEGF receptor Flk-1 blocked the effects of antidepressants on neurogenesis and behavior (Warner-Schmidt & Duman, 2007).

In addition to neurotrophic factors, serotonin signaling also provides a link between SSRIs and adult neurogenesis. Genetic and imaging studies in humans have suggested that differences in serotonin 1A receptor (5-HT1A) levels or regulation are associated with depression, anxiety and the response to antidepressants (Strobel *et al.*, 2003; Lesch & Gutknecht, 2004; Le François *et al.*, 2008). More recently, an association has been reported between a C(-1019)G polymorphism in the promoter region of the *5HT1AR* gene and a number of mood-related variables, including depression and the response to antidepressant treatment (Le François *et al.*, 2008; Fakra *et al.*, 2009). In animals, acute administration of 5-HT1A antagonists decreases cell proliferation in the adult DG (Radley & Jacobs, 2002). Mice that are deficient for 5-HT1A do not respond to fluoxetine treatment as measured by proliferation or behavior (Santarelli *et al.*, 2003). Conversely, acute or chronic treatment with the 5-HT1A agonist 8-OH-DPAT yields increased neurogenesis in the DG (Santarelli *et al.*, 2003; Banasr *et al.*, 2004). Importantly, the effect of 5-HT1A in regulating neurogenesis is likely non-cell autonomous as there is little or no expression of 5-HT1A in dividing progenitors or young adult-born neurons (Sahay *et al.*, 2007). In addition to 5-HT1A agonists, a 5-HT4 agonist has rapid, antidepressant-like effects on neurogenesis and behavior (Lucas *et al.*, 2007). However, because the newborn neurons induced by treatment would not be functionally integrated into any circuit, it is unlikely that they are responsible for the behavioral effects mediated by the 5-HT4 agonist. Additionally, 5-HT1B and 5-HT2A have also been implicated in regulating proliferation in the SGZ (Banasr *et al.*, 2004).

Another interesting possibility is that enhancement of γ-aminobutyric acid (GABA)ergic transmission may lead to the increased neurogenesis seen with SSRI treatment. GABA is well established as controlling the proliferation, dendritic complexity and synaptic integration of newborn neurons in the SGZ (Tozuka *et al.*, 2005; Ge *et al.*, 2006, 2007). Furthermore, heterozygous deletion of the γ2 subunit of $GABA_A$ receptors in immature neurons led to decreased adult neurogenesis and a depression-like behavioral phenotype (Earnheart *et al.*, 2007). Likewise, mice that are deficient for p11, a protein expressed in GABAergic interneurons in the hippocampus, are not responsive to fluoxetine treatment in either neurogenesis or behavioral readouts (Egeland *et al.*, 2010). Interestingly, acute

administration of a SSRI (citalopram) increases GABA concentration in the brains of human subjects (Bhagwagar *et al.*, 2004). Taken together, these results suggest that GABA is likely important for regulating depression-like behavior, and could also be important for mediating the effects of SSRIs on neurogenesis and mood.

Potential mechanisms underlying the requirement of neurogenesis in mediating the antidepressant response

While some work has been done that has laid a foundation for the understanding of how antidepressants increase neurogenesis, much less is known about why the increase in neurogenesis is required for the antidepressant response. One likely mechanism would be negative feedback regulation of the HPA axis and the stress response (Fig. 1). Consistent with this hypothesis, a recent study demonstrated that in mice with ablation of neurogenesis there was an increased HPA axis response to an acute stress (Schloesser *et al.*, 2009). Because stimulation of the subiculum, CA3 or DG can yield an inhibitory effect on the HPA axis (Dunn & Orr, 1984) through well-described circuitry (Herman *et al.*, 2003, 2005; Jankord & Herman, 2008), it is possible that young neurons may contribute to hippocampal-dependent negative feedback of the HPA axis (Fig. 1). Future studies will need to use genetic methods to more directly determine if young neurons impact the negative feedback circuit to the HPA axis.

Another hypothesis, which is not mutually exclusive, that has gained traction is whether neurogenesis in different areas of the SGZ plays distinct roles in the regulation of mood. Due to participation in different circuitry, it has been suggested that the dorsal and ventral hippocampus may be distinct structures (Moser & Moser, 1998; Fanselow & Dong, 2010). In the hippocampus, the dorsal DG receives inputs from lateral and caudomedial entorhinal cortex and medially located cells of the medial septal nucleus (Sahay & Hen, 2007). Outputs of the dorsal hippocampus are to the mammillary complex, dorsal lateral septum and lateral entorhinal cortex. In contrast, the ventral DG receives inputs from the rostromedial entorhinal cortex and laterally located cells of the medial septal nucleus, while ventral hippocampus outputs are to the prefrontal cortex, amygdala, nucleus accumbens, hypothalamus, medial entorhinal cortex, bed nucleus of stria terminalis, and rostral and ventral lateral septum (Sahay & Hen, 2007). This different circuitry may suggest that the dorsal hippocampus is more important for learning and memory while the ventral hippocampus is more involved in emotion (Moser & Moser, 1998; Sahay & Hen, 2007; Fanselow & Dong, 2010). Some lesion studies have supported this hypothesis (Moser *et al.*, 1993, 1995; Kjelstrup *et al.*, 2002; McHugh *et al.*, 2004). Based on this work, it has been proposed that neurogenesis along the dorsal–ventral axis may also play distinct roles in learning and mood (Sahay & Hen, 2007). In this idea, the main effect of neurogenesis in the antidepressant response would be on circuitry through ventral structures (Fig. 1). Genetic models and ablation techniques that are restricted to dorsal or ventral SGZ need to be developed in order to test this hypothesis.

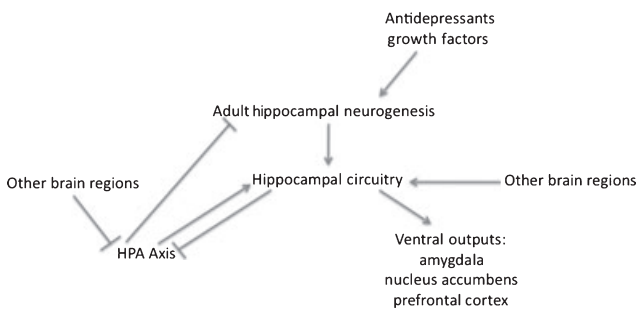

FIG. 1. Neurogenesis and the antidepressant response. Antidepressants and growth factors are well established to increase adult hippocampal neurogenesis. The change in neurogenesis levels impacts local circuitry in the DG and the hippocampus, which may contribute to the negative feedback the hippocampus elicits over the HPA axis. This may be partially responsible for the role neurogenesis plays in antidepressant-induced changes in mood. Additionally, ventral hippocampal outputs to areas such as amygdala, nucleus accumbens and prefrontal cortex that are associated with the regulation of mood could also be modulated by changes in adult neurogenesis. Conversely, stress will activate the HPA axis and lead to decreased levels of adult hippocampal neurogenesis as well as mediating multiple effects on the local circuitry in the hippocampus.

Much work has been done to advance the understanding of the synaptic and physiological properties of the young neurons, and these unique properties allow for distinguishing young neurons from their mature granule neuron counterparts (Ming & Song, 2005; Li *et al.*, 2009). Of particular relevance to antidepressant treatment is a form of long-term potentiation derived from a weak stimulation paradigm in the absence of GABA blockers [artificial cerebrospinal fluid - long term potentiation(ACSF-LTP)] that is sensitive to manipulations that block hippocampal neurogenesis (Snyder *et al.*, 2001; Saxe *et al.*, 2006; Wang *et al.*, 2008). After chronic, but not acute, fluoxetine treatment, ACSF-LTP is enhanced in sham animals and completely blocked in animals subjected to X-irradiation (Wang *et al.*, 2008), suggesting an effect of fluoxetine on the electrophysiological properties of young neurons that have integrated into the hippocampal circuitry.

Relatively little work has addressed the function of young neurons in an intact hippocampal circuit *in vivo*. In hippocampal slice work, it has been demonstrated that fluoxetine treatment enhances activity of the DG relative to CA1 in a neurogenesis-dependent manner (Airan *et al.*, 2007), suggesting a network effect of the young neurons. Furthermore, one very recent study used multiple methods to ablate adult neurogenesis *in vivo* and assessed hippocampal activity (Lacefield *et al.*, 2010). In anesthetized mice after X-irradiation or thymidine kinase-mediated pharmacogenetic ablation, perforant-path-evoked responses were reduced in magnitude. In striking contrast, there was an increase in the amplitude of spontaneous gamma-frequency bursts in the DG and hilus, as well as increased synchronization of dentate neuron firing to these bursts. This striking result may suggest that the young neurons can serve to modulate activity in the much larger population of mature granule cells rather than acting solely as independent encoding units (Lacefield *et al.*, 2010). One could imagine that antidepressant treatment may modulate hippocampal circuitry by enhancing this effect of the young neurons on the mature granule neurons, but this possibility remains to be tested.

Models of depression

Depression model selection is critical for producing coherent results when studying the role of adult neurogenesis in depression and the antidepressant response. When using mice to study adult neurogenesis, strain selection is of critical importance (Sahay & Hen, 2007; Miller *et al.*, 2008). In general, much work has determined that relative levels of adult neurogenesis across strains are very variable (Kempermann *et al.*, 1997; Kempermann & Gage, 2002); 129/SvEv mice are generally quite anxious and at baseline have low levels of proliferation in the adult DG, they will generally respond to chronic antidepressant treatment, as determined by increased neurogenesis and behavioral responses in tests such as NSF (Santarelli *et al.*, 2003). Furthermore, behavioral effects of antidepressants in 129/SvEv mice

are abolished in neurogenesis ablation models (Santarelli *et al.*, 2003). However, in another very anxious strain of mice, BALB/c, chronic antidepressant treatment does not stimulate proliferation in the DG, and antidepressant-induced behavioral effects are not neurogenesis-dependent in non-stressed mice (Holick *et al.*, 2008), while exposure to chronic unpredictable stress renders the effects of fluoxetine neurogenesis-dependent (Surget *et al.*, 2008). Less anxious mouse strains may also be useful for the study of antidepressants and neurogenesis. C57BL/6 mice show relatively higher levels of proliferation in the adult DG at baseline than 129/SvEv mice and are generally less anxious. Most C57BL/6 mice are non-responders at baseline, as chronic antidepressant treatment has little effect on neurogenesis or behavioral tests requiring chronic treatment such as NSF. However, if C57BL/6 mice are exposed to chronic stress paradigms (discussed below), a depression-like state can be induced as determined by multiple behavioral tests (David *et al.*, 2009). Chronically stressed C57BL/6 mice also display decreased adult hippocampal neurogenesis. Subsequent chronic antidepressant treatment will rescue the behavioral and neurogenesis effects of chronic stress in C57BL/6 mice (David *et al.*, 2009). In other words, chronic stress paradigms can convert C57BL/6 mice from non-responders to responders. Chronic stress paradigms can also induce a depression-like behavior in CD-1 mice (David *et al.*, 2009). For a table summarizing the effects of antidepressants in different strains of mice subjected to different types of stress, please see a recent review from David and colleagues (2010).

There are multiple chronic stress-related paradigms that can be used to induce depression-related disorders in animals that are responsive to antidepressant treatment. Given that depression in humans is very heterogeneous, there is unlikely to be one single paradigm or genetic model that will accurately replicate depression in rodents. Instead it is necessary to take a multidisciplinary approach that will ultimately combine the beneficial aspects of several different paradigms to further our understanding of the causes and progression of the disease and how to improve treatment. Unpredictable chronic mild stress (UCMS) is one commonly used paradigm (Willner, 1997; Porsolt, 2000). Importantly, UCMS has been effectively used to investigate the requirement for neurogenesis in antidepressant treatment (Surget *et al.*, 2008). In this study, UCMS effectively decreased proliferation in the DG and induced a state of anxiety as measured by the NSF test and the splash test of grooming. Fluoxetine and imipramine effectively reversed the neurogenesis and behavior phenotypes in sham but not irradiated mice (Surget *et al.*, 2008). UCMS is therefore a useful paradigm for studying the effects of neurogenesis in the antidepressant response. Potential negatives of the UCMS paradigm are that it is notoriously labor-intensive and can be difficult to establish. Furthermore, the depression-related state is usually transient, and it has been characterized that gene expression changes seen in major depressive disorders in humans are replicated by UCMS in mice in the amygdala, but not the cingulate cortex (Sibille *et al.*, 2009).

A second useful paradigm for inducing depression-like states in animals would be chronic corticosterone treatment. Long-term exposure to exogenous corticosterone has been successfully used to induce depression-like changes in behavior, neurochemistry and, importantly, proliferation in the adult DG (Ardayfio & Kim, 2006; Gourley *et al.*, 2008; Murray *et al.*, 2008). As mentioned above, chronic corticosterone has been used to induce depression-related states in both C57BL/6 and CD-1 mice (David *et al.*, 2009). Furthermore, these effects are reversible by antidepressant treatment (David *et al.*, 2009). Importantly, using X-irradiation, this study demonstrated that some but not all of the effects of antidepressant treatment were neurogenesis-dependent. More specifically, fluoxetine-induced reversal of anxiety measures in the NSF test is neurogenesis-dependent, while reversal in the open field is neurogenesis-independent (David *et al.*, 2009). Taken together, these data suggest that chronic corticosterone is also a useful paradigm for studying the effects of antidepressants. Compared with UCMS, chronic corticosterone is much less labor intensive (the corticosterone is placed in the animals' drinking water). Potential negatives of the chronic corticosterone paradigm are that it may not be useful for studying the role of the HPA axis in the neurogenesis-mediated effects of antidepressants because chronic exogenous corticosterone leads to blunting of the HPA axis (David *et al.*, 2009).

One other potentially interesting paradigm for inducing depression-related phenotypes in mice is the social defeat paradigm (Tsankova *et al.*, 2006; Krishnan *et al.*, 2007; Krishnan & Nestler, 2008). In this paradigm a mouse is forced into the territory of a mouse from a larger, more aggressive strain leading to an interaction resulting in intruder subordination. Repeated defeats over 10 days will result in a long-lasting reduced social interaction and some phenotypes reminiscent of depression (Berton *et al.*, 2006; Tsankova *et al.*, 2006; Krishnan *et al.*, 2007; Krishnan & Nestler, 2008). While this paradigm has been used extensively for studying mesolimbic dopamine circuitry, it does result in sustained changes in chromatin in the hippocampus that are modifiable by antidepressant treatment (Tsankova *et al.*, 2006). Interestingly, the beneficial effects of environmental enrichment following social defeat are neurogenesis-dependent (Schloesser *et al.*, 2010), and ablation of neurogenesis has an effect on social avoidance following social defeat (Lagace *et al.*, 2010). It will be intriguing to test the role of neurogenesis in mediating the antidepressant response in animals exposed to social defeat.

In most of these paradigms it has been difficult to dissociate anxiety from depression. While anxiety and depression do have a high comorbidity in patients, they are distinct psychiatric disorders likely caused by dysfunction of distinct brain circuitry (Nestler & Hyman, 2010). Also, many of the behavioral tests used in animals are more relevant for modeling anxiety-related than depression-related behavior. Furthermore, tests often associated with depression, such as forced swim or tail suspension, are based solely on pharmacological validity (they offer predictive capability as to whether a drug has antidepressant properties), but offer little face validity (they do not test for any signs of depression). Future work will need to pay closer attention to this distinction. It is also important to note that these paradigms have only been well characterized in male rodents. In some animal models, such as BDNF ±/− and 5-HT1A deficiency, there are clear gender differences in anxiety and depression-related behaviors (Ramboz *et al.*, 1998; Monteggia *et al.*, 2007). BDNF ±/− mice also display gender differences in vulnerability to stress, although this was only validated behaviorally in the forced swim test (Advani *et al.*, 2009). Because in humans the female population is more prone to depressive disorders, this is an important caveat when considering animal models.

Revisiting the neurogenesis hypothesis of depression

The neurogenesis hypothesis of depression postulated that a decrease in the production of newborn granule cells in the DG is related to the pathophysiology of depression, while enhanced hippocampal neurogenesis is required for the beneficial effects of antidepressant treatment. With few exceptions (Bergami *et al.*, 2008; Revest *et al.*, 2009), in most studies ablation of hippocampal neurogenesis alone is not sufficient to induce a phenotype reminiscent of either anxiety or depression (Santarelli *et al.*, 2003; Meshi *et al.*, 2006; Saxe *et al.*, 2006; Airan *et al.*, 2007; Sahay & Hen, 2007; Holick *et al.*, 2008; Surget *et al.*, 2008; Zhao *et al.*, 2008). It is also unlikely that decreased

neurogenesis could account for the volumetric decreases seen in the hippocampus of depressed patients, as X-irradiation of mouse hippocampus does not yield a significant reduction (Santarelli *et al.*, 2003). Whether specific manipulations that increase hippocampal neurogenesis alone result in a 'non-depressed' phenotype remains to be tested. However, evidence is strong that neurogenesis is required for at least some of the beneficial effects of antidepressant treatment. It will be critical for future work to determine how the addition of new units to the dentate is involved in mediating the effects of antidepressants.

It will also be critical for future work to validate the importance of antidepressant-induced neurogenesis in translational studies in humans. It will be important to test if biomarkers (such as CBV and MRS) are increased in patients treated with antidepressants. Furthermore, it may be interesting to correlate rates of neurogenesis as measured by these biomarkers with improvement of depressive signs and symptoms.

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Abbreviations

5-HT1A, serotonin 1A receptor; ACSF-LTP, artificial cerebrospinal fluid – long term potentiation; BDNF, brain-derived neurotrophic factor; BrdU, bromodeoxyuridine; CBV, cerebral blood volume; DG, dentate gyrus; ECS, electroconvulsive seizure; GABA, γ-aminobutyric acid; HPA, hypothalamic–pituitary–adrenal; MRS, magnetic resonance spectroscopy; NSF, novelty suppressed feeding; SGZ, subgranular zone; SSRI, selective serotonin reuptake inhibitor; SVZ, subventricular zone; TCAs, tricyclics; UCMS, unpredictable chronic mild stress; VEGF, vascular endothelial growth factor.

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