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Regulation of adult hippocampal neurogenesis: relevance to depression

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Recent hypotheses suggest that depression may involve an inability to mount adaptive structural changes in key neuronal networks. In particular, the addition of new neurons within the hippocampus, a limbic region implicated in mood disorders, is compromised in animal models of depression. Adult hippocampal neurogenesis is also a target for chronic antidepressant treatments, and an increase in adult hippocampal neurogenesis is implicated in the behavioral effects of antidepressants in animal models. The 'neurogenic' hypothesis of depression raises the intriguing possibility that hippocampal neurogenesis may contribute to the pathogenesis and treatment of depressive disorders. While there remains substantial debate about the precise relevance of hippocampal neurogenesis to mood disorders, this provocative hypothesis has been the focus of many recent studies. In this review, we discuss the pathways that may mediate the effects of depression models and antidepressants on adult hippocampal neurogenesis, and the promise of these studies in the development of novel antidepressants.

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Depression is a complex, syndromal psychiatric disorder that afflicts more than 20% of the population worldwide [1]. Despite the availability of effective antidepressant treatments, first discovered serendipitously over 50 years ago, the pathogenesis of depressive disorders remains poorly understood. Recently, it has been hypothesized that depression may involve the failure of adaptive plasticity in key neuronal networks [2]. Amongst the limbic brain regions implicated to exhibit such a failure of adaptive plasticity is the hippocampus. The hippocampus retains the ability to exhibit neurogenesis throughout adult life and this form of structural plasticity has been postulated to be compromised in depression and to serve as a target for antidepressants [1,3,4]. The neurogenic hypothesis of depression suggests that decreased hippocampal neurogenesis may contribute to the pathogenesis of depressive disorders, whereas enhanced hippocampal neurogenesis may contribute to the therapeutic effects of antidepressants [3,4]. The purpose of this review is to discuss the regulation of adult hippocampal neurogenesis, and the relevance of this regulation to depressive disorders.

Adult hippocampal neurogenesis

Neurogenic niches persist within the adult mammalian brain and retain the ability to generate new neurons throughout life [5,6]. Amongst the major neurogenic sites in the adult brain are the subventricular zone (SVZ) lining the lateral ventricles and the subgranular zone (SGZ) in the hippocampus. Within the hippocampus, the adult progenitors reside in the SGZ along the border between the granule cell layer and the hilus (FIGURE 1) [7]. According to one estimate, as many as 9000 progenitors divide daily in the rodent SGZ [8]. Of the dividing newborn cells that persist (~50%) as many as 85% ultimately assume a neuronal fate within approximately 3–4 weeks (FIGURE 1F). These newborn neurons transit through several stages defined by specific markers (FIGURE 1D & E) and recapitulate aspects observed during hippocampal development, with the early presence of giant depolarizing potentials allowing for activity-dependent survival, recruitment and remodeling [5,9]. The newly generated neurons in the SGZ migrate into the adjacent granule cell layer and integrate into the hippocampal circuitry receiving afferents

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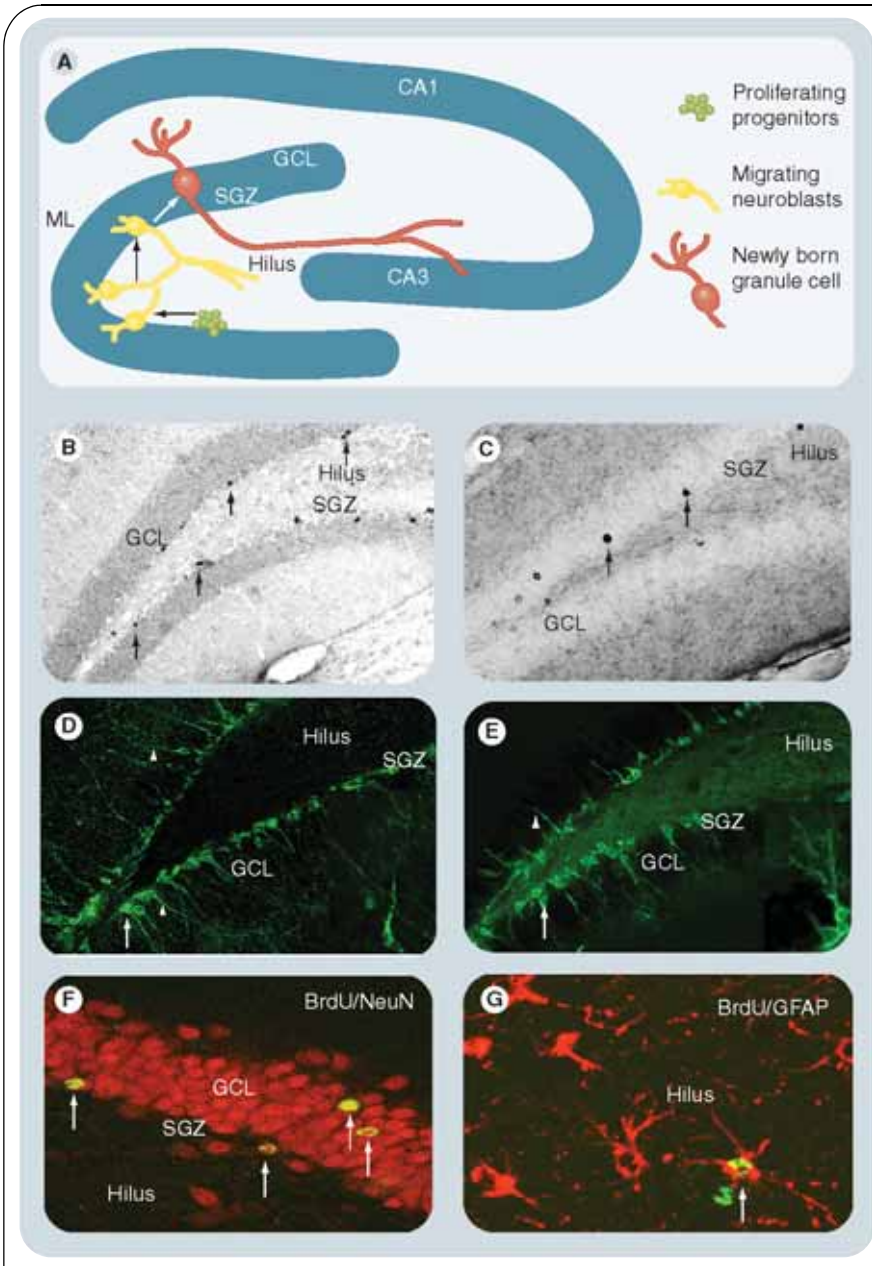

Figure 1. Neurogenesis in the hippocampus of adult rat brain. (A) Schematic of the hippocampus showing the stages of neurogenesis. Progenitors (green) divide along the inner border of the dentate gyrus known as the SGZ. The progenitors give rise to neuroblasts (yellow) that migrate into the granule cell layer and within 3 weeks differentiate into granule cells (red). Newly born granule cells extend processes into the molecular layer and CA3 region. (B) Example of BrdU-positive (arrows) dividing progenitors in the subgranular region of the dentate gyrus. BrdU-positive cells at the proliferating stage are irregular in shape and are found in clusters. (C) Example of BrdU-positive cells (arrows) 3 weeks after BrdU incorporation. Cells at this stage are oval, rarely seen in clusters and present in the granule cell layer with a few cells also seen in the SGZ. (D) Example of doublecortin (DCX)-positive cells (arrows) in the dentate gyrus. DCX-positive cells are present along the SGZ with arbors seen (arrowhead) in the GCL. (E) Example of polysialylated neuronal cell adhesion molecule (PSA-NCAM)-positive cells (arrows) in the dentate gyrus. PSA-NCAM-positive cells are present along the SGZ and have arbors localized (arrowhead) in the GCL. (F) Colocalization of the mitotic marker BrdU and the neuronal marker NeuN (arrows) indicates the differentiation of progenitor into neurons. (G) Colocalization of the mitotic marker BrdU and the glial marker GFAP (arrows) indicates the differentiation of progenitors into glia. Some BrdU-positive cells remain undifferentiated at this stage (arrowhead in G).
BrdU: 5-bromo-2-deoxyuridine; GCL: Granule cell layer; GFAP: Glial fibrillary acidic protein; ML: Molecular layer; NeuN: Neuronal nuclei; SGZ: Subgranular zone.

and projecting to CA3 cells along the mossy fiber pathway. The process of adult hippocampal neurogenesis, which encapsulates the proliferation of progenitors, survival and differentiation of daughter cells and functional integration of newborn neurons, is exquisitely sensitive to perturbations of the environment, both extrinsic and intrinsic [5], and can be regulated at all of the above stages. Most studies have profiled the influence of specific factors on hippocampal neurogenesis using the mitotic marker 5-bromo-2-deoxyuridine (BrdU) to label cells in the S-phase of the cell cycle. Depending on the time point of sacrifice post-BrdU treatment, one can address the regulation of proliferation (2 h) and short-term (24 h) or long-term (1–3 weeks) survival of daughter cells [6,10,11]. Unfortunately, there has been no consistent use of BrdU labeling paradigms, and different sacrifice times have made it difficult to compare across studies and to distinguish effects on the proliferation of progenitors or on the postmitotic survival of daughter cells.

Neurogenesis has been implicated in hippocampal-dependent functions such as the learning and memory of explicit information and emotional response [12,13]. It is interesting to note that factors that have a positive influence on hippocampal function, such as enriched environment [10], learning and antidepressant treatment [14], also increase neurogenesis in the hippocampus, whereas factors that impair hippocampal function, such as stress and animal models of depression, decrease hippocampal neurogenesis [15]. While many of the studies that make a link between hippocampal neurogenesis and function are based on correlative evidence [5,12], an unequivocal causal link is still missing. New neurons may provide an additional repertoire of plasticity to enable the adult brain to adapt to changing environmental cues, providing the possibility of making lasting modifications to the existent neuronal network and its cognitive and emotional functions.

Regulation of adult hippocampal neurogenesis & depression

Preclinical studies

Exposure to stress is thought to play an important role in the etiology of depression, and animal models of sustained stress

exposure recapitulate some of the symptomatology of depressive disorders [1,16]. To date, studies have generally observed a chronic stress-induced decline in adult hippocampal neurogenesis with predominant effects on the proliferation of hippocampal progenitors [15,17]. Chronic exposure to most stressors (restraint [18], isolation [19], social defeat [20], sleep deprivation [21] or mild stress [22]) target different stages of neurogenesis, with restraint and isolation stress decreasing the immediate survival of daughter cells, social defeat stress and sleep deprivation decreasing the long-term survival of daughter cells, and mild stress and sleep deprivation reducing the proliferation of adult hippocampal progenitors, thus contributing to a decline in new neuron production. However, there are also stressor-specific (acute social dominance [23]) effects that are restricted to changes in postmitotic survival of daughter cells only. In addition to physical and psychological stressors, metabolic stress (streptozotocin-induced diabetes [24]) has also been reported to result in a decline in adult hippocampal progenitor proliferation. The effects of stress on adult hippocampal neurogenesis are dependent on a number of variables, including the type, severity, number of exposures, frequency, unpredictability and controllability of a stressor [15,17,25]. The regulation of adult neurogenesis by stress also depends on the species, gender and age [26–28]. Taken together, this suggests that a myriad of factors come into play to result in the decline in adult neurogenesis that is broadly associated with sustained exposure to stress.

In addition, animal models of depression, such as learned helplessness [29] and olfactory bulbectomy [30], have also been reported to result in a decline in adult hippocampal neurogenesis through possible effects on either the proliferation of hippocampal progenitors or short-term survival of daughter cells, given that these studies addressed changes in BrdU-positive cell number 24 h after mitotic marker administration. An adverse experience early in life, such as prenatal stress [31] or maternal separation [32,33], which exhibit some of the symptoms of depressive disorders, also results in a modulation of adult hippocampal neurogenesis. However, while prenatal stress causes a decline in the long-term survival of newborn daughter cells [31], maternal separation results in a transient increase in progenitor proliferation restricted to early postnatal life [32] with reports of either no change or a decline in proliferation in adulthood [32,33]. It is particularly interesting to note that the effects of many of the above stress and animal models of depression, with the exception of olfactory bulbectomy, have been reported to result in region-specific effects on neurogenesis restricted to the hippocampal neurogenic niche, with no effects on the other major neurogenic niche, the SVZ lining the lateral ventricles [15,17,30]. Thus far, few reports have addressed the effects of stress/animal models of depression on neurogenesis observed in regions similar to the amygdala, and have reported either no change (social stress [20]) or intriguingly an increase in progenitor proliferation (olfactory bulbectomy [30]), suggesting possible opposing effects of stress on neurogenesis in limbic regions such as the hippocampus and amygdala. While preclinical studies support the hypothesis that, more often than not, a decline in adult hippocampal neurogenesis is associated with animal models of depression/stress, it is unknown at present if this decline in neurogenesis has a causal or simply a correlative role with the deficits of hippocampal functions observed in these animal models.

Is a decline in neurogenesis enough to generate at least some of the symptoms associated with the above animal models of depression? Previous work using irradiation-induced total block of hippocampal neurogenesis does not result in the classical symptoms associated with animal models of depression [6,34]. Thus, the question remains: is the link between changes in hippocampal neurogenesis seen in depression models and what are the possible consequences on hippocampal-dependent function and behaviors? A deeper understanding of the basic functions that ongoing adult hippocampal neurogenesis contributes to would allow for better experiment design to test the role of a decline in hippocampal neurogenesis on mood-related emotional and cognitive behaviors.

Clinical studies

The process of adult hippocampal neurogenesis has not been well addressed in humans, other than studies carried out on adult human neural stem cell cultures. At present, a single postmortem analysis report indicates a decline in neural progenitor proliferation in the hippocampus associated with schizophrenia, but not depression [35]. This study used Ki-67 as a marker of proliferation to address neural stem cell turnover in the hippocampus. Technical considerations, including the use of a single marker, and the variables introduced by prior medication exposure, make it difficult to conclusively interpret the results from this study. However, this study points to the need to comprehensively analyze ongoing adult hippocampal neurogenesis using a battery of stage-specific neurogenesis markers to examine whether there is indeed a decline in hippocampal neurogenesis at the level of progenitor proliferation or daughter cell survival in human depression. A recent study using retrospective birth-dating with C14 assessed cell birth and persistence in the human brain, and raises the possibility that the development of new tools may help to better address the questions of neurogenesis in depression [36].

Despite the present lack of clinical evidence linking changes in hippocampal neurogenesis with human depression, there have been several studies assessing hippocampal volume in depressed patients with conflicting reports of a reduction (10–15%) or no change in hippocampal volume [37–39]. A reduction in total hippocampal volume could be due to a variety of changes in total neuronal number, neuronal arborization and fiber tracts, neurogenesis, myelination or glial number [40]. This reduction in hippocampal volume has also been reported to correlate with cognitive dysfunction [41]. In this context, it is particularly interesting to note that, in one report, Cushing's syndrome patients showed a reversal of the reduction in hippocampal volume following normalization of cortisol levels, which was accompanied by an improvement in specific learning tasks [42]. It has been speculated that cortisol-mediated

alterations in neurogenesis may contribute to these changes, and a role for stress hormones in structural plasticity in depressed patients would be interesting to address. The emerging picture suggests that structural changes may be a component of the pathophysiology of depression. Taken together, the preclinical and clinical studies highlight the need for a careful investigation into changes in hippocampal neurogenesis that may arise in depressed patients, and the accompanying consequences on hippocampal function.

Regulation of adult hippocampal neurogenesis & antidepressants

Preclinical studies

Chronic exposure to antidepressant treatments of various classes, including electroconvulsive seizure, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, triple monoamine reuptake inhibitors, corticotropin-releasing factor (CRF) receptor antagonists and lithium, enhances adult hippocampal neurogenesis [14,43–45]. While most of these treatments, through 2 h BrdU studies [14], or using Ki-67 as an endogeneous marker of proliferation [43], appear to exert their effects on neurogenesis through a change in the proliferation of progenitors, a few reports have also used a 24-h time point after BrdU, and the increase in BrdU-positive cell number observed could arise through effects on either proliferation or short-term survival of daughter cells [14,45]. Additionally, these treatments have been shown to effect the long-term survival of daughter cells [14]. The increase in hippocampal neurogenesis requires chronic treatment, and parallels the time course required for the clinical benefits observed with chronic antidepressant treatment [14]. The glucocorticoid receptor antagonist mifepristone, which exerts rapid effects in psychotic major depression, is also capable of inducing a rapid reversal of the decline in neurogenesis caused by corticosterone treatment in rats, suggesting a parallel between time course of action and neurogenic changes [46]. Interestingly, nonpharmacological treatments such as enriched environment [10], voluntary exercise [47] and single night sleep deprivation [48], which have been reported to induce antidepressant-like behavioral changes in animal models, also result in an increase in hippocampal neurogenesis through effects on both proliferation (exercise and sleep deprivation) and survival (enriched environment). The effects of enhanced neurogenesis observed following antidepressant treatments, or through paradigms that improve depression-related behaviors, involve either an increase in proliferation or postmitotic survival of hippocampal progenitors, and in specific cases both. In the case of fluoxetine, the neurogenic effects of repeated administration of this drug have been reported to selectively involve an increase in symmetric cell divisions of an early progenitor cell class [49]. Taken together, the above studies suggest that different antidepressants may target distinct stages in the process of adult hippocampal neurogenesis to eventually enhance new neuron production. In addition, treatment with antidepressants can prevent the decline in hippocampal neurogenesis observed in animal models of depression/stress (learned helplessness [50], olfactory bulbectomy [30] or chronic mild stress [22]). Antidepressants have also been recently reported to reverse the neurogenic decline seen in models of metabolic stress [24] as well as in Down's syndrome [51] and Huntington disease (HD) mice [52], accompanied with an amelioration of the cognitive and behavioral deficits seen in the HD mice. What is particularly intriguing to note is that diverse treatments reported to have antidepressant effects in both preclinical and clinical studies appear to have in common the ability to enhance the number of new neurons being added into the hippocampus. In this context, it is noteworthy that transcranial magnetic stimulation known to exert antidepressant effects in humans does not appear to enhance adult hippocampal neurogenesis [53], raising the question of whether neurogenic changes are necessary for the mood-elevating effects of antidepressant treatments.

The importance of enhanced neurogenesis to the behavioral effects of these diverse antidepressant treatments is still unknown. X-ray-mediated disruption of the increase in hippocampal neurogenesis observed with chronic fluoxetine was sufficient to block the behavioral effects of this drug in the novelty suppressed feeding test [34]. However, a similar approach, blocking the enriched environment-induced increase in hippocampal neurogenesis, did not prevent the cognitive and anxiolytic effects of enriched environment [54]. It remains unclear how an increase in hippocampal neurogenesis that results from antidepressant treatments of diverse classes may contribute to an improvement in mood. Present hypotheses are speculative [3,4,55] and suggest possible roles in:

- The restoration of a stronger feedback control of the hypothalamus–pituitary–adrenal (HPA) axis
- The ability to alter the encoding of context for emotionally salient stimuli contributing to an improvement in response to positive contexts
- A gating influence on the output of prefrontal cortical circuits influencing emotional behaviors

However, the number of new neurons added are known to decline with age [56], and limited reports in the nonhuman primate and from human studies suggest that hippocampal neurogenesis is restricted. A key question that needs to be addressed is how do small changes in new neuron generation effect the functional output of the broader hippocampal network.

Clinical studies

At present, the effects of antidepressants on hippocampal neurogenesis in humans are unknown. However, there are reports that antidepressant medication may ameliorate the volumetric loss observed in patients suffering from post-traumatic stress disorder [57]. While it is unclear whether an increase in hippocampal neurogenesis contributes to this reversal, it remains a possibility yet to be tested. There are also studies with contradictory findings, suggesting no effect of antidepressants on hippocampal volume [58]. Given several confounding variables and the inability to compare results across studies in

the literature, it is difficult to reach a consensus on the effects of antidepressants on hippocampal volume in humans. Studies are urgently required to address whether antidepressant treatments, including cognitive therapy, can enhance hippocampal neurogenesis in humans. Although the effects of reuptake inhibitors may be difficult to study using adult human hippocampal neural stem cell cultures given the absence of monoaminergic neurons and monoamine transporters, this system may be useful for examining the possible direct effects of antidepressants that target specific serotonergic receptors, CRF receptors and cannabinoid receptors.

Factors that mediate the effects of animal models of depression & antidepressants on adult hippocampal neurogenesis

The 'neurogenic' theory of depression has raised substantial interest in identifying and understanding the factors that directly modulate adult hippocampal neurogenesis, and may mediate the effects of animal models of depression/stress and antidepressants [3,4]. The identification of pathways critical in the regulation of adult hippocampal neurogenesis will enable not only a deeper understanding of this form of structural plasticity, but also has the promise to unveil potential drug targets to directly modulate this process. Based on the present literature we discussed previously those factors reported to regulate adult hippocampal neurogenesis may be involved in the neurogenic changes seen in depression models and following antidepressant administration (FIGURE 2 & BOX 1).

Neurotransmitters

Neurotransmitters, in addition to their classical role as messengers between neurons, have been proposed to play a trophic role and regulate basal adult hippocampal neurogenesis [59–61]. Amongst these, the monoamine neurotransmitters serotonin [62] and norepinephrine [63], the amino acid neurotransmitters glutamate [64] and GABA [9], the neuropeptide neurotransmitters, neuropeptide Y (NPY) [65] and substance P [66], and the endocannabinoids [67] are all possible candidates that may contribute to the effects of animal models of depression/stress and antidepressants on adult hippocampal neurogenesis.

Serotonin is thought to exert a trophic influence on the proliferation of hippocampal progenitors [62]. Distinct serotonergic receptors have been demonstrated to modulate the long-term survival of daughter cells [68]. In particular, a key role for the 5-hydroxytryptamine $(5\text{-HT})_{1A}$ receptor in mediating the effects of fluoxetine on hippocampal neurogenesis was supported by a study in which 5-HT_{1A} receptor knockout mice demonstrated a loss of neurogenic and behavioral changes in response to chronic fluoxetine [34]. It is interesting to note that treatment with a SNRI is still capable of inducing neurogenic changes in 5-HT_{1A} receptor knockout mice [34], adding credence to the idea that antidepressants belonging to different classes may recruit diverse pathways to modulate hippocampal neurogenesis. We found that acute blockade of the $5\text{-HT}_{2A/2C}$ receptor results in a decline in hippocampal progenitor proliferation, whereas repeated administration of a $5\text{-HT}_{2A/2C}$ receptor antagonist results in an increase in hippocampal progenitor proliferation [UNPUBLISHED DATA], supporting the view that sustained blockade of this receptor may play a role in the antidepressant-like effects. Further studies are required to address the contribution of 5-HT_2, 5-HT_6 and 5-HT_7 receptors that have been implicated in antidepressant action to the neurogenic changes seen in depression models and following antidepressant treatment. Based on data from lesion studies, the other major monoamine implicated in depression, norepinephrine, has been reported to regulate hippocampal neurogenesis [63]. The idea that noradrenergic neurotransmission may modulate hippocampal neurogenesis is supported by evidence that blockade of the α_2-adrenoceptors, via blocking of the feedback-inhibition mechanism, can enhance noradrenergic levels, and results in an increased postmitotic survival and differentiation of adult hippocampal progenitors [69]. This suggests the possibility that α_2-adrenoceptor blockade may be an important target in the development of antidepressant drugs. It is possible to speculate that dysfunction of noradrenergic and serotonergic pathways may contribute to the neurogenic decline seen in depression models, whereas chronic antidepressant administration through increased monoamine levels may act to enhance adult hippocampal neurogenesis.

Glutamatergic neurotransmission has been shown to modulate multiple aspects of the process of adult hippocampal neurogenesis, including proliferation, survival and functional integration [64,70]. It has recently been demonstrated that proliferating progenitors can directly sense excitatory changes

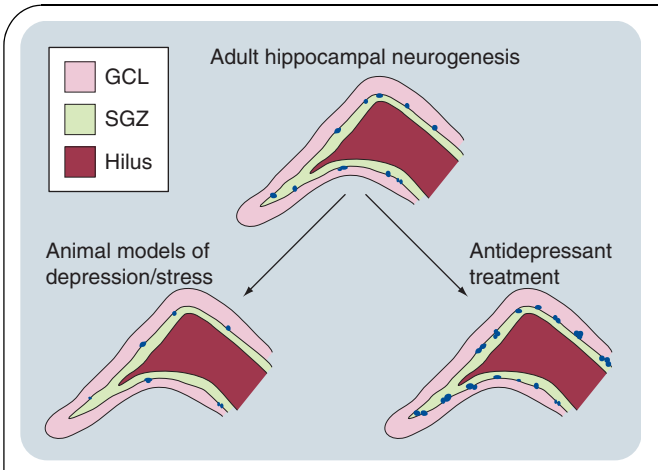

Figure 2. Regulation of adult hippocampal neurogenesis in depression models and following antidepressant treatments. The schematic illustrates the dentate gyrus subfield of the hippocampus, showing the GCL (pink), the hilus (brown) and the intermediate neurogenic site, namely the SGZ (green), which contains the adult hippocampal progenitors (blue). There is a decrease in hippocampal neurogenesis observed in animal models of depression or following sustained exposure to stress, whereas chronic treatment with diverse classes of antidepressants increases hippocampal neurogenesis. BOX 1 (shown on the next page) describes some of the factors that may mediate the neurogenic changes seen in depression models and with antidepressants. GCL: Granule cell layer; SGZ: Subgranular zone.

Box 1. Factors that may mediate the effects of depression models and antidepressant treatment on adult hippocampal neurogenesis.

Neurotransmitters

- Serotonin
- Norepinephrine
- Glutamate
- GABA
- Neuropeptide Y
- Substance P
- Endocannabinoids

Neurohormones

- Corticosterone
- Estrogen
- Thyroid

Growth factors & developmental signaling pathways

- Brain-derived neurotrophic factor
- VEGF
- IGF-1
- FGF-2
- Sonic hedgehog

Transcription factors

- cAMP response-element binding protein/activating transcription factor family

via NMDA receptors, and that this is linked to the ability to modulate NeuroD (a basic helix–loop–helix transcription factor expressed in postmitotic cells that results in a switch from proliferation to differentiation), thus resulting in an 'excitation–neurogenesis' coupling [64]. Preclinical evidence implicates the glutamatergic system, in particular the metabotropic glutamate receptors, as a novel target for antidepressant action [71,72]. Interestingly, the group II metabotropic glutamate receptor antagonist MGS0039 [72,73] and the AMPA receptor potentiator LY451646 [74], both of which have been shown to evoke antidepressant-like behaviors in animal models, also enhanced the number of BrdU-positive cells at the 24 h time point (proliferation/short-term survival) following chronic treatment. In addition, therapeutic modalities, such as electroconvulsive shock (ECS) [75] and voluntary exercise [76], which increase hippocampal neurogenesis, also increase the expression of glutamate receptors, suggesting their involvement in neurogenesis. Supporting this idea is the observation that the effect of running wheel exercise on enhanced proliferation and survival is lost in mice lacking the ε1 subunit of the NMDA receptor [77]. Glutamate has also been suggested to contribute to the effects of stress on adult hippocampal structural plasticity [70]. A conundrum that remains is the ability to evoke a role for glutamate in both the excitotoxic effects of stress, and the neuroprotective effects of enriched environment and running on adult hippocampal neurogenesis. To resolve this paradox, studies that delineate the role of individual glutamatergic receptors and address how glutamatergic neurotransmission may move from being neuroprotective to excitotoxic in the context of environmental stimuli are required.

Another major neurotransmitter that contributes to the regulation of adult hippocampal neurogenesis is the inhibitory neurotransmitter GABA [9]. The evidence of perturbed GABAergic receptor expression following stressful experiences and in animal models of depression suggests a role for this neurotransmitter in the neurogenic changes seen in depression models [71]. This possibility is supported by a recent study in which conditional mutant mice with a heterozygous inactivation of the γ2 subunit of GABA(A) receptors demonstrated a decline in hippocampal neurogenesis, through an effect on the postmitotic survival of immature neurons, accompanied with behavioral inhibition to stressful stimuli [78]. This study raises the possibility of GABA(A) receptor involvement in both the decreased neurogenesis and depressive-like behavior observed following chronic stress exposure.

In addition to the canonical neurotransmitters, the neuropeptides NPY [65] and substance P [66], as well as the endocannabinoids [67], also regulate adult hippocampal neurogenesis and are potential candidates to mediate the neurogenic changes seen in depression models and with antidepressant treatments. NPY, which is known to enhance hippocampal progenitor proliferation [65], is reduced in depression models [79], increased following antidepressant treatment [80] and can act as an antidepressant itself in animal models of depression [81]. While substance P has not been shown to modulate hippocampal neurogenesis itself, mutant mice with a disrupted neurokinin-1 receptor, the preferred receptor for substance P, exhibit both an increase in hippocampal progenitor proliferation and antidepressant-like behavior [66]. In addition, recent evidence suggests that neurokinin-1 receptor antagonists may demonstrate antidepressant-like activity [82]. The endocannabinoids, through the cannabinoid (CB)1 receptor, are thought to enhance the proliferation of adult hippocampal progenitors [67], and CB1 stimulation results in antidepressant-like behavioral effects that require an increase in hippocampal neurogenesis [83]. In addition, exposure to an endocannabinoid reuptake inhibitor reduces the predator odor-induced decline in cell proliferation and attenuates defensive burying behavior, implicating the endocannabinoid system in stress-mediated modulation of hippocampal neurogenesis [84]. The effects of endocannabinoids on other stressors need to be addressed given the conflicting reports that exist on the effects of 2,5-dihydro-2,4,5-trimethylthiazoline predator odor on progenitor proliferation [85]. Collectively, these studies suggest that multiple neurotransmitter pathways contribute to the changes in neurogenesis seen in depression models and following treatment with diverse classes of antidepressants.

Neurohormones

The stress pathway, which consists of the HPA axis, is known to be dysfunctional in approximately 50% of patients suffering from depression [1,86]. Sustained exposure to corticosterone is known to cause a decrease in adult hippocampal neurogenesis, mimicking the effects observed in animal models of stress/depression [15,17,86]. Although a causal relationship between stressors, corticosteroid release and decreased hippocampal neurogenesis remains an issue of some debate, several studies support a strong correlative link [86,87]. In addition, the chronic mild stress-induced decline in BrdU-positive cell number (progenitor proliferation/short-term survival) in the hippocampus is blocked by a CRF receptor-1 antagonist, further supporting a role for the HPA axis in the stress-induced decrease in hippocampal neurogenesis [44]. Besides a role for corticosterone in stress-mediated effects, a recent report also suggests the importance of a diurnal corticosterone rhythm in the fluoxetine-mediated increase in adult hippocampal progenitor proliferation [88].

Given the higher incidence of depressive disorders observed in women [89], and the perturbations in mood associated with premenstrual, postpartum and menopausal stages, the stimulatory influences of estrogen on adult hippocampal neurogenesis, through effects on progenitor proliferation, are particularly interesting [90]. The effects of estrogen have also been implicated in serotonergic neurotransmission [91]. The complex crosstalk between serotonin and estrogen remains poorly understood, but may contain important insights for a deeper understanding of how a gonadal hormone-like estrogen may modulate mood-related structural and behavioral changes. Future experiments are needed to address whether a loss of estrogen or perturbed estrogen receptor function contributes to an enhanced vulnerability to the development of depressive-like behaviors.

Hypothyroidism is associated with depressed mood and thyroid hormone has been implicated in augmenting the effects of antidepressant treatments [92]. Thyroid hormone is thought to positively influence adult hippocampal neurogenesis through effects on postmitotic survival and differentiation and modulate mood-related behavior [93,94]. However, the precise role of thyroid hormone receptors and the interactive effects of thyroid hormone in modulating the antidepressant action on hippocampal neurogenesis are thus far unexplored. The picture that emerges from studies of the effects of neurohormones on hippocampal neurogenesis highlights the need for deeper investigation into the role of corticosteroids, estrogen and thyroid hormone in influencing both susceptibility to mood disorders and the therapeutic outcome of antidepressant treatments.

Growth factors & developmental signaling pathways

Amongst the developmental signaling pathways, the effects of growth factors on adult hippocampal neurogenesis are the most studied [60,61]. In particular, brain-derived neurotrophic factor (BDNF) [95], VEGF [96], IGF-1 [97] and FGF-2 [98] are all known to enhance adult hippocampal neurogenesis, and have been implicated as targets of antidepressant action [82,95–97,99]. Hippocampal BDNF expression is decreased in animal models of depression/stress [32] and is enhanced in response to pharmacological antidepressants [95,100], ECS [100], enriched environment [101] and voluntary exercise [102]. In addition, BDNF itself acts as an antidepressant in animal models [103]. Furthermore, the increased survival of daughter cells seen with an enriched environment are not seen in $BDNF^{+/-}$ mice [101]. While pharmacological antidepressants still induce an increase in the proliferation of hippocampal progenitors in both $BDNF^{+/-}$ and truncated trkB receptor-overexpressing mice, they fail to produce an increase in the number of newly generated cells that persist to 3 weeks, implicating BDNF in the postmitotic survival and maintenance of immature neurons following antidepressant treatment [95]. VEGF, initially thought to modulate only angiogenesis, has been shown to play an important role in regulating hippocampal progenitor proliferation [96]. Stress-induced decreases in VEGF expression are associated with a decline in cell proliferation of progenitors closely apposed to the vasculature [104]. The evidence for a contribution of VEGF to the neurogenic increases seen following exercise and antidepressant treatment is more direct. Blockade of VEGF signaling abrogates the running-induced increase in BrdU-positive cell number (proliferation/short-term survival) [105] and prevents the increase in progenitor proliferation and behavioral effects of antidepressants such as desipramine [96]. In addition, VEGF itself exerts antidepressant-like effects [96]. IGF-1 [97] and FGF-2 [99] have been identified as targets for antidepressants based on the regulation of their expression by antidepressant treatment, as well as the reported effects of IGF-1 levels on depression-related behaviors [97,103]. Thus far, the role of these growth factors in mediating effects on neurogenesis in depression models or following antidepressant treatment remains unknown. The broad theme that emerges from the aforementioned studies is the possibility that reduced trophic signaling contributes to a decline in neurogenesis, as seen in both animal models of depression as well as following sustained stress exposure, whereas an enhanced trophic signal mediates the increased hippocampal neurogenesis, as observed in response to treatment with diverse antidepressants.

Amongst the other major developmental signaling pathways, the sonic hedgehog (Shh) pathway has been shown to be required for the maintenance of telencephalic stem cell niches in the adult brain [106]. Shh robustly increases adult hippocampal progenitor proliferation and modulates neuronal differentiation [106]. We have previously shown that blockade of Shh signaling using cyclopamine can prevent the ECS-induced increase in hippocampal progenitor proliferation [107]. However, the role of key developmental signaling pathways such as Notch, Wnt and bone morphogenic proteins in contributing to the neurogenic changes seen in depression models and with antidepressant treatment remain unexplored.

Transcription factors

The transcription factor cyclic AMP response element-binding protein (CREB) has been implicated as an important target for diverse classes of antidepressants [108]. Hippocampal CREB expression and phosphorylation is enhanced following antidepressant treatment [109] and enhanced hippocampal CREB

itself is reported to have antidepressant-like effects [110]. CREB is also known to regulate the survival and maturation of newly generated cells in the hippocampal neurogenic niche [111]. However, a causal link between CREB, antidepressants, enhanced hippocampal neurogenesis and depression-related behaviors remains to be established. Other transcription factors of the CREB/activating transcription factor family are also known to be regulated by stress and antidepressant treatments [112], however, their relevance to the neurogenic changes observed following these treatments is at present unknown.

Expert commentary

While preclinical evidence indicates a decline in hippocampal neurogenesis as being amongst the key structural changes observed in animal models of depression, the clinical evidence to support this finding is lacking [3,4]. In addition, the consequence of decreased hippocampal neurogenesis on behavior in depression models is also unclear. By contrast, the evidence for chronic antidepressant treatment-induced increases in hippocampal neurogenesis, and the relevance of such neurogenic changes to depression-related behavior, is stronger [3,4,13,32]. Many of the studies in which antidepressants were administered to normal rats reported enhanced adult hippocampal progenitor proliferation, suggesting that even baseline neurogenesis can be enhanced by antidepressant administration to animals that are not depression models. It is unclear then whether antidepressants act to enhance neurogenesis or to normalize compromised baseline neurogenesis seen in depression models. While studies on stress-induced neuronal atrophy and cell death have identified the hippocampus as a key target for the deleterious effects of stress, hippocampal structural alterations in patients suffering from depression remain a matter of substantial debate. Over the past few decades the question that has emerged from both preclinical and clinical studies is, do changes in structure within regions like the hippocampus, amygdala and prefrontal cortex, which are implicated in the neurobiology of depression, contribute to the modulation of mood-related behavior? The neurogenesis hypothesis is one component of the broader theme of structural remodeling in depressive disorders. The current status of the neurogenic hypothesis of depression is that of a provocative hypothesis which is supported at present by circumstantial evidence but lacks fundamental causal proof of the role that neurogenesis in the hippocampus may play in the modulation of mood.

Five–year view

Future preclinical studies are required to establish a causal link between changes in hippocampal neurogenesis and hippocampal-dependent cognitive and emotional behaviors. The development of mutant mice that allow a conditional, stage-specific loss of adult hippocampal progenitors would greatly facilitate this research. Such genetic tools would allow the assessment of the role of aspects of hippocampal neurogenesis, such as proliferation, postmitotic survival and functional integration, to depression-related cognitive and emotional behavioral tasks. These neurogenesis knockout mice would allow us to:

- Assess the behavioral changes that arise in the absence of hippocampal neurogenesis, and examine whether they recapitulate aspects of the symptomatology of mood disorders;
- Dissect out the relevance of adult neurogenesis to the behavioral effects of antidepressants;
- Address whether neurogenesis modulates the control of hormonal stress pathways;
- Examine whether neurogenesis is required for the encoding of context for emotionally salient cues, and modifies the outputs of prefrontal cortical and subcortical emotional circuitry.

The above experiments would allow a critical assessment of the neurogenic hypothesis of depression. Hippocampal neurogenesis has also been hypothesized to have a role in 'forgetting', thus facilitating the resetting of the hippocampus for future encoding of novel memories. If so, then impaired neurogenesis may underlie the inability to forget negative emotional contexts and the lack of flexibility in encoding positive associations [6]. This hypothesis needs experimental validation. Along with these studies, a search for novel ways to directly modulate hippocampal neurogenesis and address whether these agents act as antidepressants themselves or serve to shorten the time required for the effects of existing antidepressants on hippocampal neurogenesis and behavior would facilitate the identification of novel antidepressants. The current focus on hippocampal neurogenesis holds promise for the identification of novel drug targets for the treatment of depression [50,75].

Future clinical studies that assess whether a decline in hippocampal neurogenesis is observed in depressed patients and examine whether it contributes to hippocampal volumetric loss are required. Besides postmortem studies, the development of imaging methodology that enables the assessment of early neurogenic changes, which may occur without or precede hippocampal volumetric loss in depressed patients, would be invaluable in testing the neurogenic hypothesis. In addition, such imaging tools would allow clinical studies in patients to address whether a depression-induced decline in neurogenesis is associated with changes in contextual memory, and whether antidepressant-induced changes in neurogenesis are accompanied by the ability to encode positive context to novel stimuli. In this context, interindividual differences in stress responses to novel stimuli have been correlated with neurogenesis, with lower baseline neurogenesis associated with enhanced reactivity to novel stimuli [113]. It will be interesting to address whether antidepressant-mediated changes in neurogenesis can regulate stress-responsivity to novel cues. It is clear that substantial work is required for us to understand how adult hippocampal neurogenesis modulates mood-related behavior.

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Key issues

- Adult hippocampal neurogenesis is decreased in animal models of depression and following sustained stress exposure.
- Diverse classes of antidepressant treatments enhance adult hippocampal neurogenesis. This increase requires chronic treatment and the time course of the increase parallels the time required for the therapeutic effects of antidepressant treatment.
- Increased hippocampal neurogenesis is required for the beneficial effects of antidepressant treatments in animal models.
- Hippocampal neurogenesis has been correlated with both cognitive and emotional behaviors in animal models, but strong causal links are lacking at present.
- Thus far, there is no clinical evidence for a decrease in hippocampal neurogenesis in depressed patients or an increase following antidepressant treatment.
- Current studies suggest that diverse classes of antidepressants may recruit different pathways to mediate their neurogenic effects.
- Specific neurotransmitter pathways, neurohormones, growth factors, developmental signaling pathways and transcription factors have been reported to regulate adult hippocampal neurogenesis and are implicated as possible mediators of the neurogenic changes seen in depression models and following antidepressant treatment.
- Future preclinical and clinical studies are required to test the neurogenic theory of depression and to address the relevance of hippocampal neurogenesis to hippocampal-dependent emotional and cognitive behaviors.

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