UPDATE

Adult hippocampal neurogenesis: An actor in the antidepressant-like action

La neurogenèse hippocampique adulte : un acteur dans le mécanisme d’action des antidépresseurs

I. Mendez-David\textsuperscript{a}, R. Hen\textsuperscript{b,c}, A.M. Gardier\textsuperscript{a}, D.J. David\textsuperscript{a,*,1}

\textsuperscript{a} EA 3544 « pharmacologie des troubles anxio-dépressifs et neurogénèse », faculté de pharmacie, université Paris-Sud, Tour D1, 2\textsuperscript{e} étage, 5, rue J.-B. Clement, 92296 Chatenay-Malabry cedex, France
\textsuperscript{b} Department of psychiatry, Columbia university, New York, 10032, USA
\textsuperscript{c} Department of neuroscience, Columbia university, New York, 10032, USA

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Summary Depression and anxiety are psychiatric illnesses that are major burdens in society and affect as much as 7\% of the world’s population. The heterogeneous nature of depression suggests an involvement of multiple distinct brain regions including amygdala, prefrontal cortex and the hippocampus, which may be responsible for the diversity of the symptoms. Besides its critical role in learning and memory, the hippocampus is one of only two areas in mammalian brain where adult neurogenesis occurs. Of the current leading hypotheses of the pathophysiology and treatment of depression, the neurogenesis hypothesis of depression deserves particular attention because changes in neurogenesis are only seen after chronic, but not acute, antidepressant treatment. This review revisits the role of adult hippocampal neurogenesis in the pathophysiology of mood disorders, especially anxiety/depression, and also in the antidepressant-like responses, especially in stressed rodents.

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* Corresponding author.
E-mail address: denis.david@u-psud.fr (D.J. David).
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Introduction

Depressive and anxiety disorders are a major burden in society. Mood disorders affect 7% of the world’s population, while severe forms of depression impact 2–5% of the US population [1–3]. Furthermore, approximately 32–35 million adults in the US population (16%) experience an episode of major depression in their lifetime [1]. In Europe, a meta-analysis based on 27 eligible studies including over 150,000 subjects from 16 European countries estimated the prevalence of depression between 3 to 10% during the last 12 months [4]. The heterogeneous nature of depression suggests an involvement of multiple distinct brain regions, which may be responsible for the diverse symptoms. Human imaging and post-mortem studies of the brain have supported this hypothesis, implicating brain areas including the prefrontal and cingulate cortex, hippocampus, ventral striatum, amygdala, and thalamus [5]. Together, these brain regions operate a series of highly interacting circuits that forms a neural circuitry involved in depression [6]. The hippocampus is one of several limbic structures that have been extensively studied in individuals with psychiatric and neurologic disorders in the last decade [6,7]. Besides its critical role in learning and memory, the hippocampus is one of the only two areas in mammalian brain where adult neurogenesis occurs [7]. Adult hippocampal neurogenesis is therefore defined as the progression from neural stem cell to mature dentate granule neuron.

To fully understand the pathophysiology and treatment of depression, it is essential to delineate molecular, cellular and circuit-level changes in depressive state and also after chronic antidepressant treatment. Of the current leading hypotheses of the pathophysiology and treatment of depression, the neurogenesis hypothesis of depression deserves particular attention because changes in neurogenesis are only seen after chronic, but not acute, antidepressant treatment. This review revisits the role of adult hippocampal neurogenesis in the pathophysiology of mood disorders, especially anxiety/depression, and also in the antidepressant-like responses measured especially in stressed rodents.

Hippocampal neurogenesis

Neurogenesis refers to the production of new neurons in the brain. Originally, it was only described during development of the central nervous system. Ramon y Cajal (1913) stated that the adult brain was unable to generate new neurons. This dogma was first questioned by Altman in the 1960s, who revealed the genesis of new cells in the brain of adult rat and cat by autoradiography with tritiated thymidine [8]. Unfortunately, it was uncertain whether the new cells were actually neuronal cells. Many years later, a combination of specific neuronal markers with an analogue of thymidine, 5-bromo-2′-deoxy-uridine (BrDU), confirmed the neuronal phenotype [9]. The process of adult neurogenesis is located in two discrete brain regions: the subventricular zone (SVZ) and subgranular zone (SGZ) of dentate gyrus of the hippocampus. In this review, only the hippocampal neurogenesis and its involvement in depression will be presented.

Production of new neurons in the subgranular zone of the dentate gyrus

Hippocampal neurogenesis is possible in the SGZ of the dentate gyrus of the hippocampus because of the presence of stem cells. These stem cells evolve into neural progenitor cells that can produce multiple cell types in the central nervous system such as neurons, astrocytes, oligodendrocytes, or microglial cells. In rodents, the duration of the mitotic cycle of proliferating precursors is approximately 12 to 24 hours, leading to the production of about 8000 to 10,000 new neurons per day [10]. Given that the dentate gyrus consists of approximately one million granule cells, this phenomenon is capable of generating a little less than 1% of total granule cells each day. However, the proportion of new neurons that survive beyond 1 month is less than 50%, and the production of new cells is offset by the daily loss of mature granule cells. The surviving cells have predominantly a neuronal phenotype (75%), mainly glutamatergic granule cells, while very few are GABAergic interneuron basket cells.
Brain-derived neurotrophic factor (BDNF), depression and adult hippocampal neurogenesis

Neurotrophins, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5), are important regulators of neuronal activity, influencing a plethora of events such as neuronal differentiation, maintenance, survival, and synaptic plasticity throughout life. BDNF, a secretory glycoprotein of the neurotrophin family, is widely expressed in the adult central nervous system [11]. Like other neurotrophins, BDNF is synthesized and released in an activity-dependent manner. Studies have shown lower BDNF levels in post-mortem hippocampus of depressed patients, but higher levels in patients who are taking antidepressants at the time of death [12]. Stronger evidence for a causal role of hippocampal BDNF in the action of antidepressants comes from animal studies [13]. Direct infusion of BDNF into the dentate gyrus of the hippocampus exerted potent antidepressant effects in rodents. Furthermore, animal studies indicated that stress and chronic antidepressant treatments have opposing actions on hippocampal BDNF levels [13]. Specifically, antidepressants increase hippocampal BDNF mRNA levels, and this increase is dependent upon chronic treatment, which is consistent with the delayed onset of the therapeutic effects of antidepressants. Conversely, numerous studies have shown that different forms of stress decrease hippocampal BDNF mRNA levels [13]. Given the key role of BDNF/TrkB in mood regulation and the mechanism of action of antidepressants as reviewed earlier, a number of studies have investigated the role of BDNF/TrkB signaling in hippocampal neurogenesis. Experimental conditions that induce BDNF expression, such as physical exercise, enriched environment, and chronic antidepressant treatment, also increase hippocampal neurogenesis [14]. The survival of newborn cells is decreased in both BDNF± mice and TrkB dominant-negative mice. In addition, enriched environment failed to increase the survival of newborn cells in BDNF± mice [15]. These results suggest a role for BDNF/TrkB signaling in the survival of newborn hippocampal neurons. In contrast, there have been mixed results on the role of BDNF/TrkB signaling on hippocampal cell proliferation.

Hippocampal neurogenesis and major depression

Revisiting the neurogenesis hypothesis of depression

The neurogenic hypothesis of depression postulates that decreased production of new granule cells in the dentate gyrus of the hippocampus is linked to the pathophysiology of depression and that the increase in hippocampal neurogenesis is required for the behavioral effects of antidepressant treatment [16,17]. The few studies of hippocampal neurogenesis in depressed patients published to date have mainly relied on histological examinations of post-mortem brain tissue [18,19]. The main findings in one of these post-mortem studies are that antidepressant treatment results in an increase in the number of neural progenitors in the anterior dentate gyrus [18,20]. This was not observed in another study but these authors did not examine specifically the anterior hippocampus [19]. In both studies there was no difference between control and untreated depression. A reduction in hippocampal volume in depressed patients is somewhat established, and two meta-analyses confirmed this reduction in hippocampal volume in patients with depression using magnetic resonance imaging [21]. The length of depressive episodes coincides with the severity of the decline in hippocampal volume. However, pathophysiological studies on post-mortem brain tissue indicate that changes in the neuropil, a possible consequence of a decrease in connectivity, and glial cells may be responsible for reducing the volume of the hippocampus [22]. However, it is unlikely that such change in hippocampal volume will be difficult to determine according to the ratio between numbers of neuron provided by neurogenesis according to the total number of hippocampal neurons.

Preclinical studies in rodents, using approaches that manipulate neurogenesis, are used to establish the relationship between hippocampal neurogenesis and the behavioral effects of antidepressants in animals that are either stressed or not. Several methods to date have been developed to reduce or increase neurogenesis in rodents (Table 1):

- an X-irradiation of either the whole brain or locally in the hippocampus [16,23,24];
- asystemic treatment with an anti-mitotic agent such as methylazoxymethanol acetate (MAM) [25];
- a genetic manipulation, such as GFAP-TK mice, in which the glial fibrillary acidic protein (GFAP)-positive progenitor cells die following treatment with ganciclovir [23,26] or the inducible over-expression of pro-apoptotic gene Bax specifically in neural precursors [27].

The suppression of hippocampal neurogenesis in mice does not alter anxiety behavior in the open field or the light/dark paradigms, the elevated plus maze, or novelty suppressed feeding tests [16,23]. Thus, except one study [28], the X-irradiation in the hippocampus has no effect in the previously mentioned paradigms suggesting that the loss of hippocampal neurogenesis is not sufficient to induce a behavioral phenotype of anxiety/depression in mice, and does not exacerbate those induced by stress. Similarly, ablation of neurogenesis by a subchronic treatment with the toxin MAM, is not sufficient to induce an anhedonic behavior in rats [25].

Sahay et al. [29] developed a genetic gain of function strategy to inducibly augment the survival of adult-born neurons in a cell-autonomous manner [29]. Because 60–80% of young adult-born neurons undergo programmed cell death, for which the pro-apoptotic gene Bax is required, they used a transgenic mouse line in which the tamoxifen (TAM)-regulatable recombinase CreERT2 is expressed under the control of a 5.26-kilobase fragment of the rat nestin (Nes) gene promoter [30] together with a floxed Bax mouse line to ablale Bax selectively in neural stem cells in the adult brain and promote survival of these cells. Using this strategy, increasing adult hippocampal neurogenesis alone
Table 1  Methods used to ablate or increase neurogenesis.  
Méthodes permettant la manipulation de la neurogénèse.

<table>
<thead>
<tr>
<th>Pharmacological manipulation</th>
<th>Cranial irradiation</th>
<th>Genetic manipulation</th>
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<tbody>
<tr>
<td>5-fluorouracil (5-Fu), methylazoxymethanol (MAM), temozolomide (TMZ), cytosine arabinoside (Ara-C)</td>
<td>X-irradiation, gamma-rays</td>
<td>GFAP-TK, Nestin-TK, Nestin-Bax, Nestin Cre ERT2-Bax, TrkBlox/lax-Cre ERT2 Cyclin D2 transgenic</td>
</tr>
<tr>
<td>[23,25,35,36]</td>
<td>[16,23,24,37]</td>
<td>[26,27,29]</td>
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does not produce an anxiolytic or antidepressant-like response. However, it is important to note that this induction of neurogenesis was performed in “non-stressed animals”. Further studies will be necessary to assess whether genetic strategies designed to specifically increase adult hippocampal neurogenesis are sufficient to reverse the effects of chronic stress.

In sum, there is evidence indicating that a decreased neurogenesis is not a major factor in the development of depression, but that an increase in neurogenesis may be necessary for the behavioral effects of antidepressants [3].

**Antidepressant and adult hippocampal neurogenesis in pathological conditions**

**Animal models of depressive phenotypes**

Since no genetic variants with high penetrance that cause depression are known, animal models have mainly relied on different means of chronically exposing rodents to stressful experiences, or sensory tract lesions such as olfactory bulbectomy, to induce behavioral states that present depression-like symptoms and are responsive to chronic antidepressant treatment.

A recent procedure for inducing a depression-like state in animals is chronic glucocorticoid administration in order to mimic the effects of chronic stress. A significant proportion of depressed patients display altered activity of the hypothalamic-pituitary-adrenal (HPA) axis, and stress generally leads to hypersecretion of corticosteroids, which imposes an increased risk for depression [31]. Chronic treatment of rodents with corticosterone effectively induces multiple anxiety- and depression-like changes in behavior, neurochemistry and brain morphology [24,32,33]. Behaviorally, depression-related changes include suppression of sucrose intake and decreased self-care [33], while anxiety-related changes include:

- increased latency to emerge into the light compartment in the light/dark test;
- decreased time, entries and percent distance in the center of an open field;
- increased latency to take a bite of food in the novelty suppressed feeding (NSF) test.

**Adult hippocampal neurogenesis in pathological conditions**

Using a model based on the exogenous elevation of glucocorticoids (named the “CORT-model”), a reduction in the proliferation of progenitor cells after chronic corticosterone treatment was observed, demonstrating a role for glucocorticoids in the regulation of the proliferation stage of the neurogenic process [18]. The effects of corticosterone on neurogenesis are limited to the proliferation stage and do not involve the survival or maturation of newborn neurons. Interestingly, the effects of fluoxetine on all stages of neurogenesis (proliferation, differentiation, maturation and survival) were more pronounced in corticosterone-treated mice than in controls. It is possible that our model of corticosterone-induced stress may increase the dynamic range in which fluoxetine exerts its effects on different stages of adult hippocampal neurogenesis [24].

Agomelatine is an antidepressant drug that has a different mechanism of action from currently available antidepressants (melatonergic agonist and 5-HT2C antagonist properties). Thus, we assessed its effects on neurogenesis in the “CORT-model” of anxiety/depression [34]. Similarly to fluoxetine, chronic administration of agomelatine reversed the decrease in cell proliferation in the hippocampus without any discrimination between the dorsal and the ventral hippocampus (Table 2).

**Neurogenesis-dependent and independent effects of antidepressants**

The most compelling evidence to link adult hippocampal neurogenesis with antidepressants comes from our laboratory, in a study demonstrating that neurogenesis is necessary for the effects of imipramine, a tricyclic antidepressant, and fluoxetine, a selective serotonin reuptake inhibitor, in two mouse behavioral screens for antidepressant activity [16]. To address whether altered neurogenesis is important for the treatment of depression, Deisseroth’s group used voltage sensitive dye imaging to probe hippocampal activity in the Chronic Mild Stress in Rat. They specifically studied the role of neurogenesis in depression-relevant neurophysiology and behavior [35]. Using irradiation to ablate neurogenesis, Airan et al. also found that antidepressant behavioral efficacy in the Forced Swim Test in Rat required intact hippocampal neurogenesis. Overall, antidepressant treatment was sufficient to transiently increase
neurogenesis and exert behavioral effects long after drug clearance from the system. This effect was absent in animals lacking neurogenesis (X-ray). Recently, an elegant study in rat showed that antidepressants retain some, but not all, of their therapeutic efficacy in reducing indices of anxiety but not depression-like behavior when hippocampal neurogenesis was blocked by a cytostatic agent [36]. Indeed, using chronic mild stress (CMS) and the anti-mitotic agent MAM, authors showed that various antidepressants ameliorated CMS-induced behavioral signs of depression to the same extent in vehicle and MAM-treated animals. Conversely, using the NSF paradigm, they found that the antidepressant drugs studied (imipramine, fluoxetine) reduced the hyper-anxious state observed in CMS-exposed rats even though neurogenesis was blocked. Overall, authors concluded that antidepressants re-established neuronal plasticity in the hippocampus [36]. In the "CORT-model", using X-irradiated mice, in which hippocampal neurogenesis was abolished, we demonstrated that antidepressant treatment still elicits some anxiolytic/antidepressant-like effects. Specifically, we found that antidepressant effects in the Open Field and Forced Swim Test were neurogenesis independent, while effects in the Novelty Suppressed Feeding Test or on coat state were neurogenesis-dependent. As such, our study revealed that the behavioral effects of fluoxetine are mediated through both neurogenesis-dependent and -independent actions [24]. Previously, Surget et al. [37] presented important evidence for both neurogenesis-dependent and -independent mechanisms for the reversal of stress-induced behaviors by antidepressant drugs, including fluoxetine [37].

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

Despite all the work done that has laid a foundation for the understanding of how antidepressants increase adult hippocampal neurogenesis, much less is known about why the increase in neurogenesis is required for the antidepressant response [3]. One likely mechanism would be negative feedback regulation of the HPA axis and the stress response. It is possible that young neurons may contribute to hippocampal-dependent negative feedback of the HPA axis. One recent

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Pharmacological target</th>
<th>Phenotype</th>
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<tbody>
<tr>
<td>Fluoxetine</td>
<td>Serotonin reuptake inhibitors</td>
<td>Reversed anxiogenic/depressive-like phenotype</td>
<td>Reversed the decrease in cell proliferation induced by chronic corticosterone</td>
<td>[24,34]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No effect on the flattened circadian rhythm induced by chronic corticosterone</td>
<td>Increased all steps of adult hippocampal neurogenesis</td>
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<tr>
<td></td>
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<td></td>
<td>For all neurogenic parameters in the hippocampus: effects more pronounced in corticosterone-treated mice</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tricyclics</td>
<td>Reversed anxiogenic/depressive-like phenotype</td>
<td>Not tested</td>
<td>[24]</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>Norepinephrin reuptake inhibitors</td>
<td>Reversed anxiogenic/depressive-like phenotype</td>
<td>Not tested</td>
<td>[24]</td>
</tr>
<tr>
<td>Agomelatine</td>
<td>MT1/MT2 agonist and 5-HT2C antagonist</td>
<td>Reversed anxiogenic/depressive-like phenotype</td>
<td>Reversed the decrease in cell proliferation induced by chronic corticosterone</td>
<td>[34]</td>
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<tr>
<td></td>
<td></td>
<td>Reversed the flattened circadian rhythm induced by chronic corticosterone</td>
<td>Reversed (ventral effects for maturation)</td>
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study suggests that chronic stress severely impairs HPA axis activity and the ability of the hippocampus to modulate downstream brain areas involved in the stress response [37]. Chronic antidepressant treatment can restore the relationship between the hippocampus and the HPA axis, but only in the presence of an intact neurogenic niche. Another study also demonstrates that adult-born hippocampal neurons are required for normal expression of the endocrine and behavioral components of the stress response [38]. Future studies will need to use genetic methods to determine more directly if young neurons impact the negative feedback circuit to the HPA axis.

Another hypothesis, which is not mutually exclusive, that has gained attraction is whether neurogenesis in different areas of the SGZ play distinct roles in the regulation of mood. Due to participation in different circuitries, it has been suggested that the dorsal and ventral hippocampus may have distinct roles [39,40]. In the hippocampus of Rodents, the dorsal dentate gyrus receives inputs from lateral and caudomedial entorhinal cortex and medially located cells of the medial septal nucleus [41]. Outputs of the dorsal hippocampus are to the mammillary complex, dorsal lateral septum and lateral entorhinal cortex. In contrast, ventral dentate gyrus 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 terminals and rostral and ventral lateral septum [42]. These different anatomical circuitries suggest that the dorsal hippocampus is a more important brain area for learning and memory, while the ventral hippocampus is more involved in emotion [39,42]. In this idea, the main effect of neurogenesis in the antidepressant response would be on circuitry through ventral structures. Genetic models and ablation techniques that are restricted to dorsal or ventral SGZ need to be developed in order to test for this hypothesis.

Conclusions

The neurogenic hypothesis of mood disorders remains promising for conceptualizing depression mechanisms, which may lead to novel avenues for treatments of these psychiatric diseases [43]. Clinically, we need more information on the level and regulation of human adult hippocampal neurogenesis. Interestingly, neurogenesis decreases with age in humans and animals (Gould, 1999), whereas depression prevalence increases with age. As recently suggested by Eisch et al., more research is warranted to examine to what extent the age-induced increase in depression is due to life experience, age-induced increase in medical burden, or possibly age-induced decrease in neurogenesis [4,5,12,25]. Also, in vivo imaging of correlates of human neurogenesis is difficult, and greater technical advances are needed before we can conclude what aspects of neurogenesis structure and function are shared between humans and laboratory animals, and modulated by stress or antidepressants. Thus, it will be important to test if potential biomarkers (such as cerebral blood volume and magnetic resonance spectroscopy) [44,45] are increased in patients treated with antidepressants. Furthermore, it will be interesting to correlate rates of neurogenesis as measured by these biomarkers with improvement in depressive symptoms.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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