Antidepressant medications as regulators of adult rodent and human hippocampal neurogenesis

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SUMMARY

New neuron formation in the adult brain expands our knowledge and incorporates a novel dimension on brain plasticity. Adult neurogenesis is a complex process regulated by different factors within the niche, where adult neural stem cells reside, proliferate and differentiate. Neural stem cells, together with astrocytes and endothelial cells, form the principle components of this complex niche. Other molecular factors that regulate adult neurogenesis are neurotransmitters (GABA, glutamate, serotonin, dopamine); hormones (prolactin, growth hormone, estrogens and melatonin); growth factors (FGF, EGF, VEGF) and neurotrophins (BDNF, NT3). All of them regulate different aspects of the neurogenic process.

Behavioral regulators that influence new neuron formation in the adult brain include physical activity, complex stimulatory environment (better known as an enriched environment) and social interaction. Voluntary physical activity with free access to the running wheel increases the number of proliferating cells, while the complex stimulatory environment provided by an enriched environment preferentially influences survival of newborn cells. In addition, social interaction has a positive influence on new neuron formation in the dentate gyrus (DG).

Although adult hippocampal neurogenesis is positively regulated by the aforementioned factors, there are different conditions that have negative influences on this process. Some such conditions include stress exposure and sleep deprivation. Both conditions are present in neuro-psychiatric diseases such as depression, anxiety and schizophrenia. Thus, stress and sleep deprivation impair adult hippocampal neurogenesis.

Alteration of the neurogenic process following stress occurs due to high levels of glucocorticoid receptors within the hippocampus and because exposure to stress causes an increase in glucocorticoid levels.

Preclinical studies have shown that exposure to different classes of stressors affect hippocampal neurogenesis. Prolonged exposure to stressors (chronic mild stress), predatory odor, foot shock, acute force swimming and psychosocial stress not only affect mature neuronal plasticity but also hippocampal neurogenesis.

Although there is information about the effects of stress on adult neurogenesis, the mechanism by which stress causes inhibition of hippocampal neurogenesis remains unclear. Recent works have shown that exposure to stress increases the pro-inflammatory cytokine interleukin-1β (IL-1β) in several brain areas. Also, administration of IL-1β exerts stress-like effects including down-regulation of hippocampal brain-derived neurotrophic factor (BDNF). Additionally, inhibition of the receptor for IL-1β prevents stress-like effects. Moreover, the suppression of cell proliferation is mediated by direct actions of IL-1β on IL-1R1 receptors located in precursor cells. These findings support the fact that IL-1β is a critical mediator of the anti-neurogenic effect caused by acute and chronic stress. However, IL-1β is not the only mediator of stress that could be involved in the alteration of adult hippocampal neurogenesis. Recently it was reported that the decrease in cell proliferation concomitantly occurs with an increase of IL6 and TNFα levels.

Preclinical studies have suggested that adult hippocampal neurogenesis is not the sole cause of depression or the sole mechanism of treatment efficacy, but it is likely an important contributor to this complex disorder. In order to reverse the effects of stress on adult hippocampal neurogenesis, different therapies have been used, for example: electroconvulsive therapy (ECT), exercise, complex stimulatory environment and antidepressant drugs.

Although the most rapid induction of neurogenesis is seen with ECT application, most studies have been done with antidepressant drugs. The effects of antidepressants are time-dependent as greatest therapeutic effects are observed over the course of weeks.

Different types of antidepressants (serotonin and norepinephrine reuptake inhibitors, monoamine oxidase inhibitors and atypical antidepressants) have been used to study their influence on the neurogenic process. Despite the fact that serotonin reuptake inhibitors are the most prescribed treatments for major depression and that the therapeutic effects of antidepressants require chronic treatment, the mechanisms by which these drugs exert their effects on hippocampal neurogenesis are still unknown. Although serotonin reuptake inhibitors are very fast in increasing serotonin levels, the antidepressant action is delayed possibly because of the induction of structural or functional changes that potentially require more time (2-4 weeks).

In this regard, one of the actions of antidepressants is the regulation of adult hippocampal neurogenesis, a process that is consistent with the delayed onset of therapeutic effects of antidepressants. Fluoxetine is one of the antidepressants most used to study influence on adult neurogenesis. Fluoxetine targets amplifying neural progenitors by increasing the rate of symmetric divisions.
la formación de neuronas es un proceso regulado de manera fina la elongación axonal y la integración de las neuronas nuevas a los células madre, la proliferación de los neuroblastos, la migración involucra diferentes eventos celulares tales como: la división de las dad del encéfalo. En este sentido, la neurogénesis es un proceso que amplió el conocimiento acerca de la plastici- psychiatric disorders. clinical studies to address the role of adult neurogenesis in neuro- performed in human beings to correlate the preclinical findings with neurogesis. Here, fluoxetine also affects dendrite maturation and functional integration of new neurons. Chronic fluoxetine treatment modifies dendrite morphology increasing dendrite arborization and favors synaptic plasticity of newborn granule cells. Also, chronic administration of fluoxetine causes behavioral improvement, an effect that was blocked when neurogenesis was abated by X-ray irradiation. Another important factor that influences the effect of antide- pressants on adult neurogenesis is genetic background. Antidepressants induced behavioral improvement depending on the genetic background of the mouse strain used. Preclinical studies in mice have revealed different actions of antidepressants on adult hippocampal neurogenesis. However, studies in humans are few and deserve greater attention to discover the correlation between preclinical and clinical studies. Recent work in human brains shows contradictory evidence regarding the regulation of neuronal development by antidepressants. This evidence is in keeping with a recently published work in which it was demonstrated that the effects of ADs are age-dependent. Altogether, multiple evidence indicates that antidepressants affect several aspects of the neurogenic process. Therefore, chronic treatment is necessary for the antidepressant-dependent regulation of adult hippocampal neurogenesis. In addition, it has been shown that antidepressants act through different pathways involving both neurogenesis-dependent and neurogenesis-independent actions. Although there is significant growth in the adult hippocampal neurogenesis field, it is necessary to increase the number of studies performed in human beings to correlate the preclinical findings with clinical studies to address the role of adult neurogenesis in neuropsychiatric disorders.

Key words: Adult neurogenesis, antidepressants, stress, doublecortin.
INTRODUCTION

The discovery of the forming of new neurons in the brain during adulthood was an interesting finding that expanded our knowledge of the plasticity of the brain. In 1966, Joseph Altman used radioactive thymidine to report the presence of cells with the ability to proliferate. This study laid the groundwork for the study of neuronal regeneration in the hippocampus of the adult brain.

The neurogenic process is complex and is regulated by several factors. These factors include the niche, which is made up primarily of stem cells, astrocytes and endothelial cells. Other factors that positively regulate several events during neurogenesis include some neurotransmitters (GABA, glutamate, serotonin, dopamine), hormones (prolactin, growth hormone and melatonin), growth factors (FGF, EGF) and neurotrophins (BDNF, NT3). Likewise, another type of regulators of the neurogenic process has been described, which includes physical activity, a complex and novel environment (referred to as an «enriched environment» in literature) and social interaction.

In addition to the positive regulators of neurogenesis, regulators have also been found that negatively impact the neurogenic process. Negative factors include prolonged sleep deprivation and stress. Stress in particular plays an important role in the development of some neuropsychiatric diseases, such as schizophrenia, anxiety and depression.

NEURONAL DEVELOPMENT IN THE ADULT HIPPOCAMPUS

The adult brain has two regions in which neurons are constitutively formed. These regions are the olfactory bulb and the dentate gyrus (DG) in the hippocampus. The new neurons in the olfactory bulb are formed from stem cells that reside in the subventricular zone of the lateral ventricles. These cells divide to subsequently migrate in groups along the rostral migratory chain until reaching the olfactory bulb, where their terminal differentiation takes place.

In the hippocampus, the new neurons derive from stem cells located in the subgranular zone (SGZ) (Figure 1). Cells in the cellular proliferation stage can be identified with the use of a thymidine analog, 5-bromo-deoxyuridine (BrdU). This synthetic reagent is incorporated into the deoxyribonucleic acid (DNA) during the synthesis stage of the cell cycle and its incorporation can be detected with specific antibodies, allowing us to identify cells that have proliferated and that will become new neurons (Figures 2C and C). Once the stem cells divide, they give way to rapid amplification cells. These cells will migrate tangentially to begin differentiating into neurons, which will survive to develop dendrites that project toward the molecular layer (ML) (Figures 1A and 1B). In the ML, the dendrites of the new neurons establish connections that are important for the survival and maturation of the neurons, which leads to full integration and functionality (Figures 1A and 1B).

The stem cells from the SGZ of the DG show characteristics of radial glia, and express specific protein markers such as glial fibrillary acidic protein (GFAP) (Figures 1B, 2A and A) and nestin, a marker of non-differentiated cells (Figures 1B, 2B and B). Meanwhile, the neuroblasts, which are neural precursors, and immature neurons, which show radial dendrites, express doublecortin, a protein that is distributed in the cytoplasm and in the dendrites of the neuron (Figures 1B, 2D and D). In a more advanced maturation study, the new neurons express other protein markers: calretinin (Figures 2E and E) and calbindin. Likewise, several studies have shown that new neurons show electrical properties similar to mature neurons, which has confirmed the functionality of newly-created neurons.

STRESS AND NEURONAL DEVELOPMENT

The hippocampus is a structure of the limbic system which is altered both in structure and function in patients with neuropsychiatric disorders. Abnormalities in the hippocampus have also been observed in preclinical studies, using animal models of neuropsychiatric diseases. The processes that are thereby affected include hippocampal neurogenesis. In this regard, stress is an important factor for the presence of anxiety and for the development of major depression. Preclinical studies have revealed that the application of or exposure to different types of stress affects the neurogenic process. Based on the results of preclinical studies, it can be established that the exposure of animals to acute stressors affects primarily the proliferation of progenitor cells in the DG of the hippocampus, without largely affecting differentiation and survival. The models most used in this research include the exposure to predator odors, as well as electrical shock. Meanwhile, chronic stress models have shown that, in addition to affecting the cellular proliferation stage, cell survival and neuronal differentiation are also affected. The models most used include social chronic stress, chronic restriction of movement and chronic unpredictable stress. In addition, it is known that the use of chronic stressors affects neurogenesis produces alterations in the hypothalamic-pituitary-adrenal axis (HPA).

In summation, all kinds of stress cause alterations in neuronal plasticity, and some also affect the forming of neurons.

Contrary to what has been described regarding the effects of stress on neurogenesis, several preclinical studies...
have shown that the alterations caused by stress are reverted with different treatments, including transcranial magnetic stimulation (TMS), pharmacological treatments and even exercise and an enriched environment. Of the treatments used, TMS has been shown to have positive results in practice, especially in patients suffering from major depression. This may be due to the antidepressant effects of TMS. In light of this evidence, Czéh et al. (2002) researched the effect of applying TMS for 18 days in adult rats on hippocampal neurogenesis. This and other studies have shown that TMS is beneficial to certain stages in the process of hippocampal neurogenesis. In particular, exposure for 14 days showed an increase in the number of cells in the proliferation stage, which could suggest that the antidepressant effect of TMS may be due to the increase in neurogenesis. Although it has been proven that TMS has a positive impact on the neurogenic process, its long-term effects must be studied.

![Process of hippocampal neurogenesis in adult brain](image)

**Figure 1.** Formation of neurons in the hippocampus. Image of a coronal section dyed with cresyl violet showing the subgranular zone of the dentate gyrus (SGZ), where the neurogenic process takes place. Also, the granular layer is shown (GL), the molecular layer (ML) and the hilus. The image highlights the SGZ and the GL of the dentate gyrus. Representations are also shown of the different cellular stages of neural development based on the expression of specific markers, depending on the stage of the neurogenic process.
Antidepressant medications as regulators of hippocampal neurogenesis

On the other hand, the effect of antidepressant drugs (ADs) requires a prolonged period of time, given that the greatest effects have been seen over the course of 2 to 4 weeks.32 This type of action has been observed both with tricyclic ADs as well as serotonin reuptake inhibitors.31,32,56

While it is known that stress affects the formation of neurons in the hippocampus and this is associated with an increase in glucocorticoid levels, the mechanism underlying the inhibition of neurogenesis caused by stress was not understood until in recent studies it was shown that the exposure to stress significantly increases levels of proinflammatory cytokines interleukin-1β (IL-1β) in different regions of the brain. In addition, administering of IL-1β produces effects similar to those caused by stress, such as the alteration in the forming of neurons and decrease in BDNF levels.57-59 In the same study it was shown that IL-1β acts through its receptor (IL-1RI), which is expressed by precursor cells.57 In this way, through activation of IL-1RI, IL-1β inhibits cellular proliferation. This signaling pathway involves the transcription factor nuclear-κ-beta (NF-κB). Likewise, it has been recently shown that the decrease in cellular proliferation caused by stress also occurs in parallel with the increase in the expression of IL-6 and TNF-α messengers. Collectively, these studies indicate that the proinflammatory cytokines form part of the critical mediators of the anti-neurogenic effects caused by acute and chronic stress.60

In addition to the increase in cytokine levels, it has been reported that glucocorticoids also regulate the expression of neurotrophic factors important for hippocampal neurogenesis, including BDNF, NT-3, FGF and VEGF. In this regard, it has been observed that the expression of BDNF is affected in the DG of the hippocampus in animal models of acute and chronic stress.43,46,61-71

Likewise, it has also been observed that stress can affect neurogenesis through the activation of NMDA receptors.72-74 While the mechanism by which NMDA receptors reduce neuroplasticity is not fully understood, it is believed that high levels of glucocorticoids can produce high levels of glutamate, which in turn would provoke excitotoxicity due to the excessive intake of calcium (Ca++), compromising the viability of the cell.75

MECHANISMS INVOLVED IN THE INHIBITION OF HIPPOCAMPAL NEUROGENESIS DUE TO STRESS

Figure 2. Images showing some markers expressed during adult neural development. Panel A show glial cells identified by the expression of glial fibrillary acidic protein (GFAP). Some are located in the granular layer (GL) and show radial projections better viewed in Panel A’. Panel B shows nestin positive cells, which are found in the GL and other cells also found in the blood vessels (Panel B’). The stem and progenitor cells that incorporated bromodeoxyuridine (BrdU), indicating cellular proliferation, are shown in Panels C and C’. The neuroblasts and postmitotic neurons are shown in Panels D and D’. These cellular populations were identified with the expression of doublecortin. The neurons in a mature stage are shown in Panels E and E’. The images indicate the location of the molecular layer (ML), the subgranular zone (SGZ) and the hilus. The images in Panels A, B, D and E were taken with a 40x lens. The image from Panel C was captured with a 10x lens. The A’-E’ images were captured with a 100x lens. All images were obtained using a Leica microscope.

On the other hand, the effect of antidepressant drugs (ADs) requires a prolonged period of time, given that the greatest effects have been seen over the course of 2 to 4 weeks.32 This type of action has been observed both with tricyclic ADs as well as serotonin reuptake inhibitors.31,32,56

ANTIDEPRESSANT DRUGS AND NEUROGENESIS (PRECLINICAL STUDIES)

The findings resulting from preclinical studies have suggested that the impairment of hippocampal neurogenesis is neither the only cause of depression, nor the only mechanism by which to achieve effective treatment of this disease. However, alterations in the neurogenic process may be a significant factor in the etiology of this neuropsychiatric ailment.76 To reverse the effects of stress on the structural and functional organization of the hippocampus, some ADs have been used (Table 1).
ADs are the first-choice treatment option for major depression and their therapeutic effects can be observed after treatment of two to four weeks, which may be associated with changes in the structural and functional levels of different areas of the limbic system. In this sense, the changes in the hippocampal structure coincide with the time in which mature and functional neurons are formed.32,72-91

Prior studies have reported the effect of ADs on hippocampal neurogenesis.77-85 However, the mechanism by which ADs modulate neuronal development in the adult brain was not understood until in 2006 Encinas et al. identified the initial target of fluoxetine (FLX), a serotonin reuptake inhibitor.86 This target is a population corresponding to neuronal progenitors better known as the rapid amplification population (Figure 1). This population increases after chronic treatment with FLX, which suggests that the increase in neurogenesis caused by FLX results from the increase in the rapid expansion population.86 In addition to this, Wang et al. found that FLX also encourages dendritic maturation and the functional integration of new neurons.87 This is an interesting finding, given that it has also been shown that the maturation of the dendrites of immature neurons is controlled separately from the regulation of cellular proliferation and that microregulatory processes influence the process of neuronal formation.88 As such, chronic treatment with FLX modifies the morphology of the dendrites of new neurons by increasing the complexity of the dendritic tree and encouraging synaptic plasticity, this in addition to the positive effects on behavior (Figures 1 and 2). Behavioral effects were blocked by irradiations, which strongly supports the importance of hippocampal neurogenesis for the effects of AD drugs.87

Table 1. Information from certain reports in which the effect of antidepressant drugs on hippocampal neurogenesis in stress models was assessed

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Type</th>
<th>Daily dosage</th>
<th>Duration</th>
<th>Effect</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>SSRI</td>
<td>5 mg/kg</td>
<td>14/21</td>
<td>Proliferation</td>
<td>Rats</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg/kg</td>
<td>2-8</td>
<td></td>
<td>Stress in rats</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>MAO-I</td>
<td>10 mg/kg</td>
<td>14</td>
<td>Proliferation</td>
<td>Rats</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>NRI</td>
<td>20 mg/kg x 2</td>
<td>21</td>
<td>Proliferation</td>
<td>Rats</td>
</tr>
<tr>
<td>Rolipram</td>
<td>PDE4-I</td>
<td>1.25 mg/Kg</td>
<td>14</td>
<td></td>
<td>Mice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.25 mg/Kg</td>
<td>16-23</td>
<td>Survival</td>
<td>Mice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 mg/Kg</td>
<td>7</td>
<td>p-CREB</td>
<td>Ischemia in mice</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tricyclic</td>
<td>20 mg/kg</td>
<td>20-21</td>
<td>Proliferation</td>
<td>Rats</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg/kg</td>
<td>14</td>
<td>Survival</td>
<td>Transgenic mice</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>SSRI</td>
<td>5 mg/kg</td>
<td>28</td>
<td>Proliferation</td>
<td>CMS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg/kg</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agomelatine</td>
<td>Melatonergic and SHT inhibitor</td>
<td>40 mg/kg</td>
<td>15/2</td>
<td>Proliferation</td>
<td>Rats</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SSRI: selective serotonin reuptake inhibitor; MAO-I: monoamine oxidase inhibitor; NRI: norepinephrine reuptake inhibitor; PDE4-I: phosphodiesterase-4 inhibitor; CMS: chronic mild stress.

There are also studies in which other types of ADs have been used, which found that regardless of the type of ADs used, these drugs modulate the neurogenic process (Table 1).77-85 Thus, the results from all these studies support the theory that ADs modulate different events in the neurogenic process.

Another important factor for observing the effects of ADs on neurogenesis and behavior is genetic inheritance.84 Studies in which radiation was used to abate cellular proliferation, in addition to evaluation of specific behaviors related to depression, did not reveal correlations between the decrease in cellular proliferation and the behavioral effects caused by the ADs.79,89,91 This indicates that the actions of ADs occur through different mechanisms, which may or may not involve alterations in the neurogenic process. That being said, it is important to point out that the effects of ADs will depend on genetic inheritance and the strain of mice used.90

NEUROTROPHINS AND GROWTH FACTORS AS MODULATORS OF THE EFFECT OF ANTIDEPRESSANT DRUGS

AD drugs modulate different stages of the neurogenic process, increasing expression levels of neurotrophins and growth factors.31,86,87,92 An example of this can be found in the increase of the expression of messengers of BDNF and its receptor, trkB (receptor tyrosine kinase B) in the hippocampus.93,94 In addition, it has also been shown that ADs increase BDNF levels at the protein level in postmortem brains in patients diagnosed with depression.95 Likewise,
ADs increase the activation of trkB, which is related to the increase in the release of BDNF in the prefrontal cortex and the hippocampus.96 It has also been observed that the infusion of BDNF in the hippocampus produces antidepressant effects in mice.97,98 Finally, a recent study confirmed that ADs require the BDNF pathway to produce their positive effects on neurogenesis. This observation was based on the use of transgenic rats that show decreases in the BDNF signaling pathway. In this case, ADs were unable to induce an antidepressive response, nor could they produce a positive effect on neurogenesis.96 This data indicates that BDNF is important in order for ADs to encourage neurogenesis in the hippocampus of the adult brain.

In addition to BDNF, VEGF also acts as a modulator of the effect of ADs on neurogenesis. Recently, it was shown that ADs increase levels of VEGF, and encourage cellular proliferation and the development of antidepressive behaviors.99,100 Likewise, in this study it was shown that the effects of VEGF occur through the activation of its receptor, Flk-1.99,100

Collectively, the aforementioned studies indicate that ADs require certain neurotrophins and growth factors to modulate their effects on neuronal development in the adult brain.

**Antidepressant drugs and hippocampal neurogenesis in humans**

The neurogenic process in the hippocampus during adulthood also occurs in the human brain. In 1988, Eriksson et al. found new neurons in the human hippocampus. In addition, the neurogenic process in humans has been described as following stages similar to those observed in the brains of mice.2,20

Regarding the role of ADs in the neurogenic process in humans, two studies were recently published in which it was revealed that both tricyclic ADs and selective serotonin reuptake inhibitors affect hippocampal neurogenesis in humans.101,102 In the study by Boldrini et al. it was found that ADs increased the number of neuronal precursor cells and the volume of the DG in subjects diagnosed with major depression and that were under 38 years of age.103 Meanwhile, the study by Lucassen et al. revealed the presence of histone-3- and MCM2-positive cells (minichromosome maintenance protein-2); both are markers of cells in cellular division. However, ADs did not encourage cellular proliferation in the DG of the hippocampus in geriatric patients.102 In addition, a decrease was found in the number of cells in cellular proliferation in relation to the age of the subjects studied.102 Although both studies are interesting, they cannot be compared, since there are important variations in the patients and in the subjects from the control groups. These variations include the limited size of the samples and the potential impact of underlying conditions which some subjects in the control group presented. In addition, both studies differ in age group, whereas Lucassen et al. has an average age of 68, Boldrini used a range between 17 and 67 years of age, most certainly a significant factor in human neurogenesis.101-105 In a way, both studies confirm that ADs affect several processes in the adult brain, which include neurogenesis. In addition, these studies confirm that the effects of ADs are dependent on age.96-98 Finally, these efforts provide evidence on the regulation of the first stage of the neurogenic process. However, we still do not know whether ADs also affect other stages of neurogenesis. For that reason, the use of technology could help in conducting a better analysis of the neurogenic process in humans.106 In this regard, magnetic resonance spectroscopy may be an important tool for detecting biomarkers of cellular proliferation in the hippocampus. In addition, the inclusion of healthy subjects for control groups and the application of strict inclusion criteria would allow us to better study the role of neurogenesis in neuropsychiatric disorders.107 Finally, it would also be interesting to determine whether the increase in hippocampal neurogenesis in humans is associated with a decrease in symptoms of major depressive disorder.103

**Conclusions**

The forming of neurons offers an example of the plasticity of the adult brain. This process is regulated by several factors, including stress, which is a key element in some affective disorders. The studies cited in this review have provided evidence of the role of hippocampal neurogenesis in depression. Likewise, these studies show that the effects of stress are reversed by ADs. Likewise, it has been revealed that the effects of ADs occur through mechanisms both dependent and independent of hippocampal neurogenesis. In this regard, genetic inheritance plays an important role, give the complexity in the genetic control of hippocampal neurogenesis.90

Despite progress made in the field of hippocampal neurogenesis, additional work is needed to apply the findings of preclinical studies to clinical studies. Such clinical studies may support the theories proposed regarding the role of neurogenesis in the adult hippocampus and its relation to neuropsychiatric disorders. In this regard, closer collaboration is needed between basic and clinical researchers in order to prove the proposed hypotheses, given that better-controlled clinical studies are required to conduct an improved assessment of the potential role of the alteration of the neurogenic process in depression and other neuropsychiatric ailments.108-110

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