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Role of NMDA Receptors in Adult-generated Hippocampal Neurons: Implications for Alleviating Depression and Anxiety-like Behaviors

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Abstract. The hippocampus is the brain region critical for learning, memory and emotional regulation. New neurons are continuously produced in the dentate gyrus of the hippocampus throughout adulthood and evidence from animal studies suggest the involvement of adult hippocampal neurogenesis in mental health, particularly in conditions like major depressive disorder (MDD) and memory formation. Selective serotonin reuptake inhibitors (SSRIs), a common class of antidepressants, have been shown to enhance neurogenesis, while disrupted neurogenesis is linked to cognitive impairments and decreased stress resilience in animal studies. Research supports the notion that NMDA receptors are essential in neurogenesis, regulating neuronal plasticity and synaptogenesis. Patients with MDD often exhibit decreased cognitive ability and memory, implicating NMDA receptor involvement. While NMDA receptors are considered potential drug targets for mental illnesses, evidence linking NMDA receptor activity in adult hippocampal neurogenesis (AHN) to mental health is limited, and the mechanisms remain poorly understood. This review aims to summarize recent studies to elucidate the connection between NMDA receptors on adult-born neurons and stress resilience, highlighting their potential as therapeutic targets for depression and anxiety-like behaviors..

Keywords: NMDA receptor, adult-born hippocampal neurons, neurogenesis, stress resilience, depression.

1. Introduction

Depression and anxiety disorders are among the most prevalent mental health conditions worldwide, contributing significantly to the global burden of disease and leading to disability and impaired quality of life [1]. Patients with major depressive disorder (MDD) are commonly observed with reduced brain volumes and are present with symptoms of reduced cognitive ability and poor memory, suggesting a link to neurodegeneration and subsequently impaired neurogenesis[2]. Stress is a significant risk factor for these mental disorders, with chronic stress shown to reduce neurogenesis, leading to depressive symptoms, whereas high stress resilience in individuals demonstrate improved mental health outcomes [3,4]. Most antidepressant drugs work by blocking the reabsorption of serotonin and norepinephrine so they remain in the synaptic cleft for longer, eliciting positive effects on mood [5]. Recent studies have discovered that antidepressant drugs can also promote neurogenesis in the adult hippocampus, this may explain why 1/3 of the affected population do not respond to traditional antidepressant drugs due to

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other factors influencing adult hippocampal neurogenesis in individuals [6-8]. Additionally, emerging studies targeting the NMDA receptor has shown its potent effect in regulating mood and behavior [9]. This has led to the idea that NMDA receptors may play a role in depression and anxiety-like symptoms by mediating adult hippocampal neurogenesis (AHN).

AHN is the process by which new neurons are generated in the adult hippocampus, playing important roles in learning and memory. Neurogenesis begins with the proliferation of neural stem cells in the dentate gyrus driven by signaling factors, followed by differentiation of neuroblasts and migration to integrate into the existing circuit [10]. New neurons can mature and survive if synaptic connections are formed with other neurons in the hippocampus, this process of synaptogenesis is influenced by neuronal activity specifically regulated by the NMDA receptor. Environmental conditions, age, stress, and other factors also contribute to the survival of adult-born neurons. Upon maturation, adult-born neurons become integrated into the hippocampus circuit contributing to the overall function of the region. These new neurons exhibit a high degree of plasticity, which is thought to be associated with improved learning and memory abilities and linked to mood regulation [11].

The NMDA receptor is a class of ion channel on the membrane of all neurons, important in mediating synaptic plasticity. When activated by glutamate, NMDA receptor allows Ca^{2+} ions to enter the neuron, activating intracellular signaling pathways to control gene expression of the neuron. Long term potentiation (LTP) occurs when the synaptic strength is enhanced for a long period through NMDA receptor activation and is considered the major mechanisms underlying learning and memory; subsequently, NMDA receptors can weaken synaptic strength to finetune the circuit through long term depression (LTD)[12]. Several knock out studies in mice have shown the effect of NMDA receptors in regulating the survival of immature granule cells, promoting the idea that NMDA receptors may play an important role in AHN's anti-depressant like activity [13].

To establish a direct causality between NMDA receptor activity on adult-born neurons and its ability to alleviate depressive phenotypes, this review will first introduce the discovery of increased neurogenesis as a result of anti-depressant drug administration. It will then focus on the role of NMDA receptors involved in adult hippocampal neurogenesis and regulating mood, with findings demonstrating the link between receptor activity and altered cognitive function. Finally, the significance of stress as a risk factor of depression and its effect on NMDA receptors will be discussed to suggest their importance in improving mood through neurogenesis regulation.

2. Role of Neurogenesis in Eliciting Antidepressant Effects

Due to reported hippocampal volume reduction in patients suffering from depression, anxiety, and schizophrenia, many studies have focused on the hypothesis proposed by Duman that neurogenesis can be linked to depressive behaviors in individuals [14]. The administration of SSRIs was first discovered to increase neurogenesis in 2000 by Malberg and colleagues [8]. By chronically administering a range of different antidepressants to adult mice, they found a significant increase in BrdU-labelled cells in the dentate gyrus of the hippocampus, indicating enhanced adult neurogenesis. This phenomenon was only observed after the chronic administration of antidepressants for over 14 days and not with acute drug administration, matching the delayed time course for antidepressants to show behavioral improvements [8,15]. This time frame remains consistent for newborn cells in the dentate gyrus to become fully mature, as these cells become functionally integrated into the existing hippocampal circuit at about 2 weeks of their development [16]. Malberg's results suggest that the mechanisms underlying the therapeutic effects of antidepressants may involve enhanced neurogenesis by reversing stress-induced neuronal loss in MDD patients. It was later discovered that AHN is required for antidepressants to elicit their behavioral effects; without neurogenesis, subjects showed no response to chronic drug administration [7]. Santarelli and colleagues inhibited neurogenesis in adult mice by irradiation to demonstrate the significance of AHN in mediating antidepressant behavioral responses. Their results showed that, without the formation of new neurons in the adult hippocampus, these mice showed no response to chronic fluoxetine administration and no improved performance in the behavioral assays conducted [7]. This evidence indicates that the improved behavioral effects of antidepressant treatment are dependent on adult

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neurogenesis in the hippocampus, and AHN is potentially associated with the baseline stress resilience of the subject.

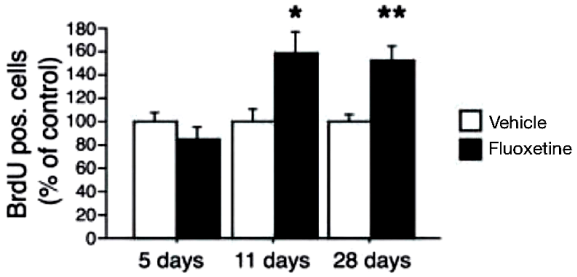


Figure 1. Adapted from previous paper [7]. Number of BrdU-positive dividing cells significantly increases after chronic Fluoxetine administration (>11 days) relative to the control group. Fluoxetine increases neurogenesis.

Recent studies have proven that AHN alone can produce some degree of stress resilience in rodents; more importantly, it is the activity of these newborn neurons in the hippocampus that elicits the response. Hill proposed the hypothesis that increasing neurogenesis alone, without the administration of antidepressants, can prevent the behavioral effects of stress in rodents. Their study was conducted using Bax knockout (KO) mice to promote adult neural stem cell survival and observing the behavioral changes of KO mice under chronic corticosterone (CORT) administration as a model of stress [6]. As expected, Bax deletion promotes neurogenesis, and more mature AHNs were found in the hippocampus. This leads to elevated stress resilience, shown through normal behavioral assay performance under chronic stress, no different from those mice in the control group [6]. This study demonstrated that increased neurogenesis reduces stress-induced anxiety and depression-like behaviors in rodents. A different study conducted by Anacker and colleagues used chemogenetics and optogenetics to control the level of neurogenesis in the adult mice hippocampus. Their findings showed that increasing neurogenesis improved performance in behavioral assays through inhibition of stress-responsive cells in the ventral dentate gyrus [17]. These findings provide some insight into the neural mechanisms underlying stress resilience and the importance of AHN in regulating affective behavior.

Further study suggests that newborn hippocampal neuron activity may be the actual key in antidepressants' efficacy to alleviate depressive behaviors. Selective activation of newborn neurons in rodents showed decreased anxiety and depressive-like phenotypes in behavioral assays and enhanced the antidepressant activity of Fluoxetine [18]. This study suggests that the number of newborn neurons does not play a big role in stress resilience; an increase in the excitability of newborn hippocampal neurons is sufficient to mediate baseline stress resilience in rodents and can further enhance the antidepressant effects of Fluoxetine [18].

3. NMDA Receptor Activity Influences Neurogenesis

Accumulating evidence has highlighted the importance of NMDA receptor activity in supporting the normal process of neurogenesis by maintaining the survival and migration of neurons [13,19]. The hypothesis that the survival of AHN neurons is dependent on their input activity, which is largely regulated by NMDA receptors, has been proven to be mostly true, though the specific mechanisms remain unclear. Many recent studies have confirmed that NMDA receptor activity is crucial for the survival of newborn neurons, and its deletion in these neurons leads to severe effects [19,20].

By using NR1 NMDA subunit knockout mice, Tashiro et al. proved that NMDA receptors play an important role in maintaining the survival of newborn neurons after 2 weeks of their development [20], suggesting their involvement in the functional integration into the circuit to receive input from other neurons. They found that newborn neurons lacking NMDA receptors showed impaired synaptic activity and died prematurely, indicating that synaptic activity serves as a selection mechanism regulated by NMDA receptors. Only newborn neurons that have been functionally integrated into the circuit with the help of NMDA receptors can survive [20]. Similarly, NMDA receptor KO mice showed a significant

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reduction in neurogenesis and the size of the granule cell layer of the dentate gyrus in adult mice [13]. The reduction in neurogenesis in KO NR1 mice is linked with NMDA receptor function in supporting the survival of neuroblasts; blocking its activity increases neuroblast apoptosis [21]. These findings demonstrate the importance of NMDA receptors in regulating the normal process of neurogenesis, from supporting the proliferation of neural stem cells to maintaining the survival and integration of newborn cells. Additionally, NMDA receptors have been shown to regulate the normal migration of newborn neurons in the dentate gyrus. The inhibition of NMDA receptor activity using antagonists in a different study showed similar results of decreased proliferating cells and over-migration of newborn neurons in the dentate gyrus [22]. Their results demonstrated an abnormal migration of neurons in the absence of NMDA activity; without being in the right position in the hippocampus, these newborn neurons cannot form functional synapses, speeding up their apoptosis. These findings support the link between NMDA receptor activity and depressive behavior through the regulation of neurogenesis.

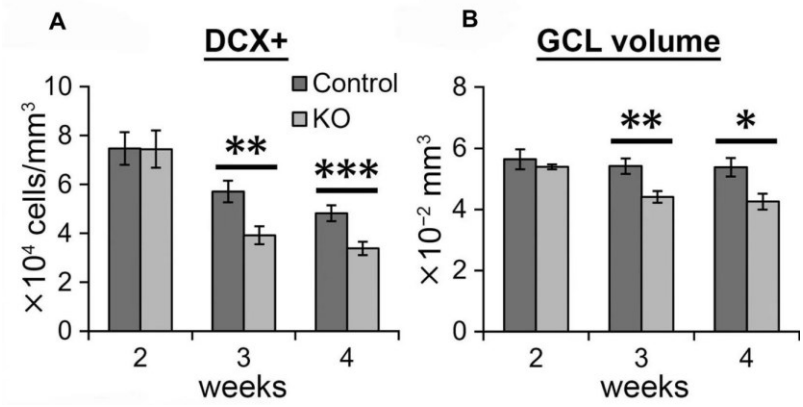


Figure 2. Adapted from pervious paper [13]. Neurogenesis significantly impaired in the dentate gyrus of NR1 KO mice over 2 weeks old. A) Density of DCX+ labelled immature granule cells in control and KO mice; B) Granule cell layer of the dentate gyrus in control and KO mice.

4. Evidence of NMDA Receptor Involvement in Mood Regulation

Growing pre-clinical studies suggest the role of the NMDA class glutamate system in the pathophysiology of depression and mechanisms of antidepressants, with NMDA receptor antagonists showing effective behavior in animals [23]. In behavioral assays, NMDA receptor impairment results in significant changes in behavior in the open field test and novelty-suppressed feeding test (NSF) [13]. NMDA receptor KO mice showed longer latency to feed and explored the center of the cage more frequently in the NSF test, reflecting a higher degree of anxiety; this impairment in behavior is directly related to the absence of NMDA receptor activity [13]. The first pre-clinical study done on humans showed the effect of the NMDA receptor antagonist ketamine hydrochloride in decreasing depressive symptoms and improving mood [23]. Further studies have also confirmed the rapid and prolonged antidepressant effect of NMDA antagonists acting on the prefrontal cortex of the brain [24]. Though animal studies and pre-clinical human trials show contrasts in the mechanisms of NMDA receptor activity in improving behavior, the hypothesis of NMDA receptor dysfunction in mental disorders is proven to be true [23].

Treatments targeting synaptic plasticity also show an improvement in the behavioral performance of animals under stress [25]. This indicates the involvement of NMDA receptors in stress resilience, as neural plasticity is primarily regulated by NMDA activity. The mechanism of ketamine's antidepressant effect was later discovered by Li et al., where improved mood was associated with an increase in synaptic number, dendritic spine density, and synaptic function in the prefrontal cortex [26]. Ketamine is shown to increase glutamate levels in the medial prefrontal cortex, leading to an increased phosphorylation of cAMP-response element binding (CREB), which changes cell expression to facilitate synaptic plasticity. This pathway is commonly associated with the NMDA receptor [26]. The

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discovery of the effects and mechanisms of ketamine suggests that NMDA receptors are important targets for antidepressant drugs [25,26]. An improvement in depressive behavior following psilocybin was observed in rodent studies. Mice given the psychedelic drug underwent increased gene expression associated with neural plasticity and showed increased synaptic budding PSD95 in both the hippocampus and prefrontal cortex [27]. Though studies are yet to directly prove the relevance of NMDA receptors specifically on newborn neurons in mood regulation, these data point us to the possibility of NMDA's ability to improve affective behavior through neural plasticity.

5. Stress Affects NMDA Receptor Activity

In models of chronic stress, rodents often present with high depression and anxiety-like behaviors, associating stress with higher risks of mental disorders. When post-natal mice are separated from their mothers, a common stress model, it results in lower levels of neurotrophic factor BDNF and NMDA receptor subunits in their hippocampus, both strong drivers of neurogenesis [28]. This suggests that stress impacts the development of behavior and stress response in rodents, possibly through impairments in neural plasticity and neurogenesis [28]. These findings demonstrate that early life stress can result in lasting impairment in stress resilience due to reduced BDNF and NMDA receptor levels. Independent of NMDA receptors, prolonged exposure to stress can cause a reduction in synaptic density and dendritic branching in the hippocampus, indicating impairments in the regulation of LTP and LTD, leading to decreased neurogenesis [25].

An additional study conducted by Pickering and colleagues showed similar findings, where chronic maternal separation in post-natal mice causes a change in the gene expression of NMDA receptor subunit NR2B and other glutamate receptors [29]. Mice under chronic stress had reduced expression of functional NMDA receptors and also showed a decrease in expression of AMPA receptors, suggesting that chronic stress leads to long-term damage in signal transduction and neuron survival, as observed through the significant reduction in neuronal density in the dentate gyrus, marking an impairment in neurogenesis [29]. It was proposed that chronic stress increases glutamate release. This overproduction of the excitatory neurotransmitter may have led to increased neuronal apoptosis due to exposure to excitotoxicity, explaining the changes in expression of glutamate receptors in the hippocampus [29]. Overall, exposure to chronic stress at a young age leads to changes in the expression of glutamate receptors in the hippocampus of rodents, suggesting a link with future complications in stress resilience.

6. Discussions

Though the mechanisms remain unknown, it is clear that NMDA receptors play an important role in neurogenesis in the adult hippocampus and their subsequent impact on depression and anxiety-like behaviors. The evidence presented in this review highlights the critical involvement of NMDA receptors in regulating the survival, integration, and functionality of these new neurons, which are essential for regulating affective behaviors and cognitive functions in rodents. Interestingly, increased neurogenesis alone is sufficient to regulate the baseline level of stress resilience in rodents and shows improved mood and behaviors in stress models. NMDA receptors can also facilitate synaptic plasticity through LTP and LTD, which underlies the mechanisms for learning and memory. The disruption in synaptic plasticity is associated with impaired neurogenesis and enhanced depression and anxiety-like behaviors. This evidence altogether suggests that enhancing NMDA receptor activity can promote neurogenesis and synaptic plasticity, both leading to improved behavioral outcomes, confirming the hypothesis of NMDA receptor involvement in mood regulation.

Interestingly, common SSRI class antidepressants enhance neurogenesis, either as the desired direct outcome of drug administration or as a side effect that enhances their antidepressant effect in animals. The delayed effect of antidepressant drugs indicates that additional mechanisms may be at play. NMDA receptor antagonists such as ketamine and other psychedelics show rapid antidepressant effects by promoting synaptic plasticity and neurogenesis, offering a promising alternative for treatment-resistant depression and highlighting the link between NMDA receptor activity and mood regulation in depressive behaviors [26].

Future research should aim to look into the precise mechanisms by which NMDA receptors influence the survival and integration of newborn neurons. Understanding the signalling pathways controlled by NMDA receptor activity provides a deeper insight into their role in neurogenesis and could possibly establish a causality between NMDA receptor activity and depressive behaviors. The findings indicate specific roles for different NMDA receptor subunits (N2A, N2B). Under specific cases like induced stress or NMDA receptor antagonist administration, only one subunit is found to be affected in rodents, suggesting potential targeted therapies that could minimize side effects and enhance therapeutic efficacy in patients. Furthermore, studies using NMDA receptor antagonists showed rapid and long-lasting antidepressant effects, offering ideas for fast-acting novel therapeutics for mental disorders.

7. Conclusion

This review provides evidence of the antidepressant effects of neurogenesis and newborn neuron activity and the importance of NMDA receptors in mediating these processes as potential therapeutic targets for mental disorders. However, future studies are needed to gain a deeper understanding of the molecular mechanisms of how NMDA receptors can regulate these processes for stress resilience. This is important to establish a direct link to target newborn neurons in the hippocampus and its glutamate receptors as potential novel therapeutics for mental disorders.

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