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Pathophysiology of Hippocampal Neurogenesis

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Abstract

Background: The hippocampus plays a crucial role in producing and maintaining neurons through neurogenesis, which persists into adulthood and is vital for emotional regulation. Neurogenesis in the dentate gyrus of the hippocampus is central to understanding emotional disorders, particularly stress and depression. Research shows that stress reduces neurogenesis, leading to hippocampal atrophy, which is associated with emotional disorders. Antidepressants can reverse this effect, promoting neurogenesis and reducing atrophy. Animal studies indicate that neurogenesis is essential for the efficacy of antidepressant treatments, making it a key target for understanding psychiatric disorders. This study aims to explore the relationship between hippocampal neurogenesis, stress, and antidepressant treatments. Specifically, it investigates how neurogenesis is affected by various stress levels and antidepressant therapies in the context of psychiatric disorders.

Methods: A review of existing clinical and preclinical studies was conducted to assess the effects of stress and antidepressants on neurogenesis, focusing on animal models and human studies of depression.

Results: Stress reduces hippocampal neurogenesis, contributing to depression-like behavior. Antidepressant treatments, particularly those involving serotonin and noradrenaline, increase neurogenesis, reversing stress-induced neuronal damage. Moreover, neurogenesis appears essential for the therapeutic efficacy of antidepressants.

Conclusion: Hippocampal neurogenesis is a key factor in the regulation of emotional behavior and response to stress. Antidepressant treatments support neurogenesis, providing therapeutic benefits in depression, but further research is needed to explore its full potential in neuropsychiatric treatment. Understanding the neurogenic mechanisms underlying depression can enhance therapeutic approaches, particularly for stress-induced mood disorders.

Keywords: hippocampal neurogenesis; stress; depression; antidepressants; dentate gyrus; brain-derived neurotrophic factor.

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Introduction

Depression, a widespread neuropsychiatric disorder, affects millions globally. It is associated with dysfunction in several brain regions, particularly the hippocampus, which plays a significant role in mood regulation. Depression manifests through cognitive distortions, behavioral fluctuations, and disturbances in basic drives like sleep and appetite. The hippocampus' ability to produce new neurons, a process termed neurogenesis, diminishes with chronic stress, contributing to the disorder. Neurogenesis in the dentate gyrus of the hippocampus is crucial for reversing stress-induced damage, and antidepressant therapies show potential for boosting this process. This study aims to review hippocampal neurogenesis, the impact of stress and depression, and the role of antidepressants in neurogenic regulation.

Materials and Methods

The study primarily uses a review-based approach, synthesizing existing literature on hippocampal neurogenesis, stress, and depression. Animal models, particularly rodent studies, are emphasized to explore the role of neurogenesis in behavioral responses and treatment efficacy. Key studies examining how antidepressants, stress hormones (glucocorticoids, serotonin, and noradrenaline), and brain-derived neurotrophic factor (BDNF) modulate hippocampal activity are reviewed. Imaging studies and post-mortem analyses of human brains are also incorporated to assess hippocampal volume changes in depressed individuals.

Statistical Analysis

Various studies cited within this review used animal models to quantitatively assess changes in hippocampal neurogenesis under stress and antidepressant treatment. Techniques like BrdU labeling and imaging (MRI) were used to measure the proliferation, survival, and integration of neurons. Statistical comparisons were made between stressed and non-stressed groups, as well as between treatment types (e.g., SSRIs, TCAs, and antipsychotics). Behavioral changes were analyzed in terms of antidepressant-induced shifts in neurogenesis, with significance tested using tools such as the forced swim test and novelty-suppressed feeding models.

Results

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Chronic stress was consistently shown to inhibit neurogenesis in the hippocampus, leading to structural atrophy and reduced functional capacity, correlating with depressive behaviors in both animal models and human studies. Conversely, chronic administration of antidepressants—specifically those that enhance serotonin and noradrenaline signaling—boosted neurogenesis and reversed stress-induced neuronal damage. The necessity of neurogenesis for the antidepressant response was confirmed through experiments involving irradiation to block neurogenesis, which suppressed the behavioral efficacy of antidepressants. Moreover, neurotrophic factors like BDNF and VEGF were critical for promoting neuronal survival and integration in antidepressant-treated subjects.

Discussion

Depression is typically defined as a fluctuating neuropsychiatric disorder that affects approximately 5% of the global population, with a higher prevalence in females[1]. It is a heterogeneous condition, involving multiple distinct limbic regions of the brain. This complexity leads to a wide range of symptoms, which can be classified into three main categories:

1. Cognitive distortions (e.g., suicidal thoughts, guilt),
2. Behavioral changes (e.g., sadness, irritability),
3. Disruptions in basic drives[2] (e.g., eating, sleeping).

The hippocampus is considered a key brain structure involved in depression, with several processes contributing to its development:

1. Increased concentration of stress-responsive adrenal glucocorticoid receptors,
2. Hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis (a significant marker of depression),
3. Impaired negative feedback regulation of the HPA axis by the hippocampus, affecting glucocorticoid release[3],
4. Reduced neurogenesis or hippocampal atrophy due to chronic stress or elevated glucocorticoid levels, further weakening feedback inhibition of the HPA axis[4],
5. Interactions between the prefrontal cortex and amygdala—both involved in emotion and cognition—and the hippocampus.

Neurogenesis refers to the production of new neurons from immature precursor cells, occurring in a stepwise manner. It starts with precursor cell proliferation, morphological differentiation, and ends with the creation of functional neurons[3].

In adults, neurogenesis takes place in the dentate gyrus (DG) of the hippocampus, specifically in the subgranular zone (SGZ). The area contains stem cells that may differentiate into neurons, oligodendrocytes, microglial cells, or astrocytes. Neurons are the predominant cells formed, migrating to the granule cell layer (GCL) to develop into excitatory granule cells (Figure 1)[5].

Stem cells in the central nervous system (CNS) are characterized by their high proliferative capacity and multipotency, and they eventually develop into progenitor cells with more specialized functions. These progenitors differentiate into either neuronal or glial cells[6].

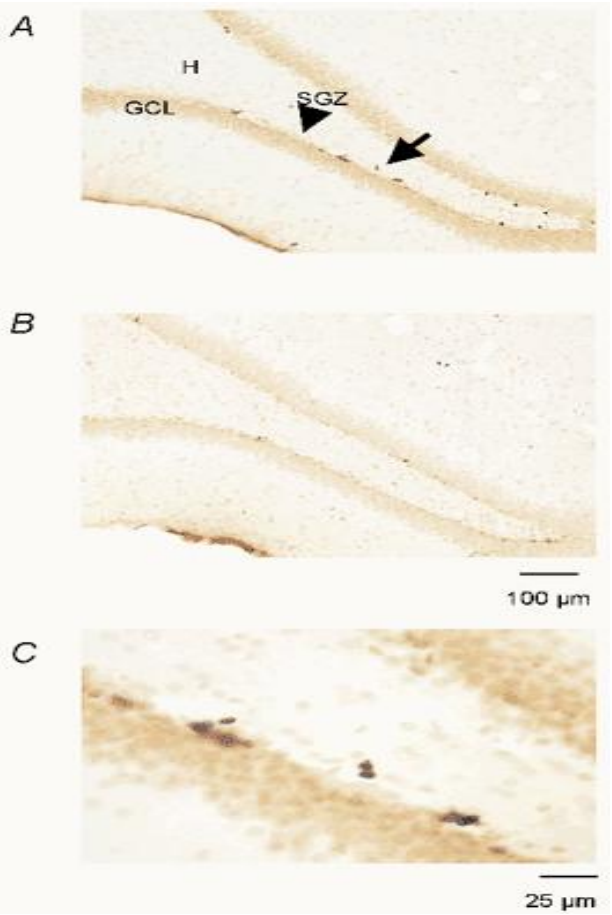

Figure 1. Photomicrograph of the hippocampal DG. BrdU labelling highlights proliferating cells in the SGZ (arrowhead, A). Higher magnification shows cells migrating to the SGZ in C[11].

In the SGZ, two main types of precursor cells exist: type 1 and type 2 (subdivided into type 2a and type 2b). Type 1 cells are radial glial-like neural stem cells, while type 2a and 2b cells show astrocytic traits[7]. Some type 2 cells are GABAergic, receiving synaptic input[8]. Type 2b cells, identified by doublecortin (DCX) expression and a horizontal morphology, differ from the radial type 2a cells. DCX expression persists from the proliferative to maturation phases. Type 2 cells are pivotal in converting glial cells into the neuronal lineage. Type 2b cells express the markers Prox1 and NEUROD1, with Prox1 being essential for granule cell formation.

In rat models, SOX2, a transcription factor in the adult SGZ, is critical for stem cell maintenance by inhibiting neuronal differentiation. Studies show that type 1 cells express high levels of SOX2 and rarely divide, forming the bulk of quiescent cells. As type 2a cells transition to type 2b, SOX2 expression decreases, but DCX remains. These highly proliferative type 2b cells contribute to oligodendrocyte production[9].

Amplifying neural progenitors (ANPs) are daughter cells produced from quiescent progenitors through asymmetric division, expressing both nestin (an intermediate filament in most progenitor cells) and SOX.

Radial glial-like cells' mitotic activity can be tracked using the 5-bromo-3'-deoxyuridine (BrdU) staining protocol, a

synthetic thymidine analog incorporated during DNA synthesis in the S phase. This method revealed that over 90% of proliferating cells are type 2, while type 1 cells contribute minimally[10].

The overlap between neuronal and glial traits in progenitor cells can lead to either neuronal or glial formation, depending on whether the progenitor is amplifying or quiescent[12].

New neurons express markers like calretinin and specific neuronal nuclear protein (NeuN) after exiting the cell cycle[13]. Many cells die if they fail to connect to the molecular layer, but those that do form dendrites and axons and synapse with CA3 pyramidal neurons. Initial maturation is marked by high input resistance, low membrane capacitance, and excitatory GABAergic inputs essential for dendrite development. Over the next three weeks, they develop glutamatergic inputs and dendritic spines, transitioning to inhibitory connections. Granule cells begin generating action potentials at around seven weeks, completing electrophysiological maturation. The integration of these neurons into existing brain networks is regulated by NMDA-type glutamate receptors.

During this stage, around 80% of granule cells are post-mitotic, marked by DCX expression, while the rest are proliferating neuroblasts. These cells, aged between 1 and 28 days, express calretinin during the early post-mitotic phase, which lasts about 3-4 weeks and correlates with dendrite maturation. Dendritic branching follows axonal synapsing with CA3 neurons[14]. As cells mature, they shift from expressing calretinin to calbindin, a marker of mature granule cells that indicates their increasing electrophysiological similarity to fully developed neurons. The complete maturation process is linked to memory formation and storage[15].

The rate of hippocampal neurogenesis declines significantly with age, contributing to reduced dentate gyrus growth. Animal studies show this decline is due to decreased cell proliferation, migration, and differentiation into the granule cell layer[16].

Stress reduces adult hippocampal neurogenesis by decreasing cell proliferation in the SGZ and reducing the survival of newly generated neurons. Both acute and chronic stress similarly impair neurogenesis. Stress also reduces the branching and length of CA3 pyramidal neurons, contributing to hippocampal atrophy and depression (Figure 2)[17]. Stress regulates hippocampal plasticity by lowering BDNF levels. This affects dendritic branching and synaptic reorganization in CA1 and CA3 neurons, as well as cell proliferation in the SGZ[18].

Animal studies show that stress (via restraint, foot shock, and immobilization) decreases neurogenesis, while antidepressants like fluoxetine, moclobemide, and tianeptine reverse this effect, increasing hippocampal volume, BDNF, and dendritic branching[19].

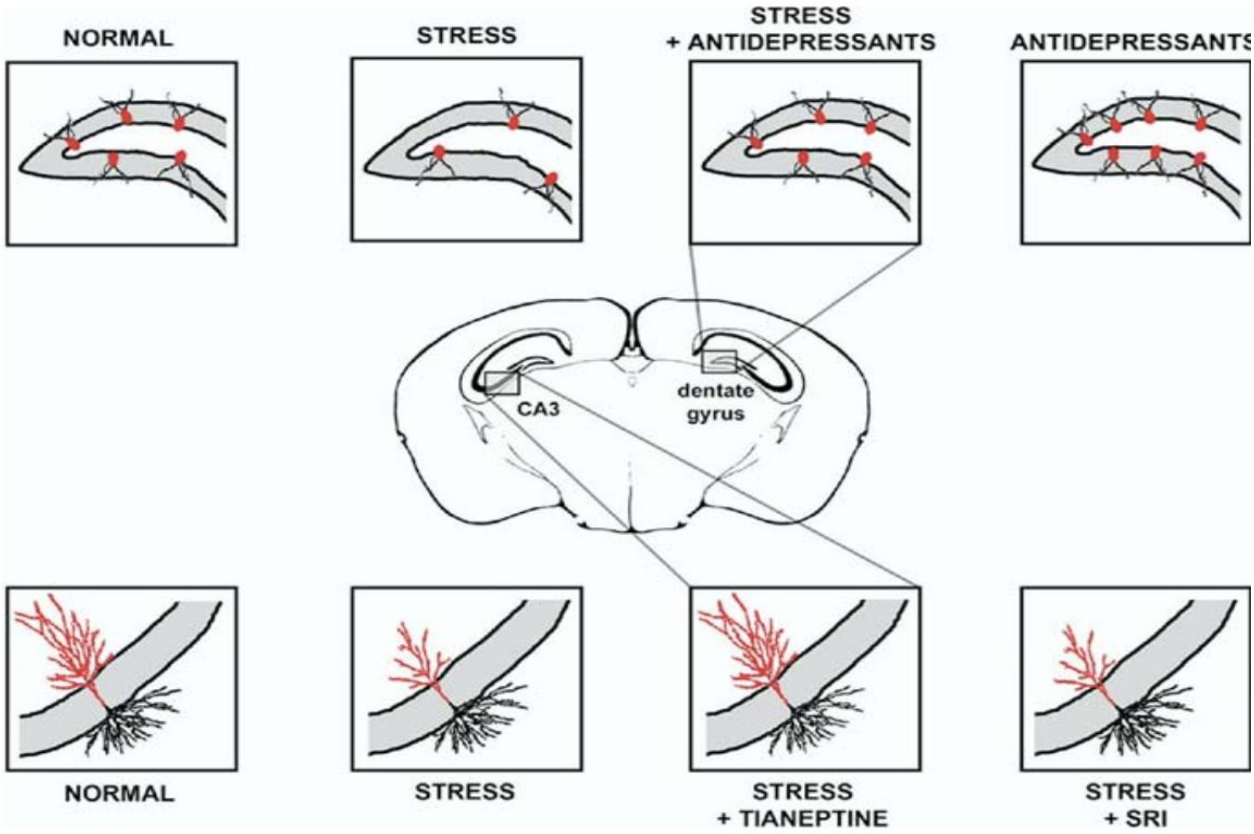

Figure 2. Coronal section of a mouse brain showing neurogenesis and effects of stress and antidepressants. Top panels highlight the dentate gyrus, with dendritic projections (black) in the granule cell layer and newly formed neurons (red) in the subgranular layer. Stress reduces neurogenesis, while antidepressants increase it, reversing stress effects. Bottom panels show a CA3 pyramidal neuron with basal (red) and apical (black) dendrites. Stress reduces apical dendrite growth, reversed by tianeptine, while SRIs have no effect[19].

The molecular basis of similar hippocampal changes from both selective serotonin reuptake inhibitors (SSRIs) and enhancers (SSREs) remains unclear, but both likely promote cellular and structural plasticity, mitigating stress[20].

Stress hormones, particularly glucocorticoids, regulate hippocampal downregulation via the HPA axis, affecting cell proliferation, differentiation, and survival. Removal of the adrenal glands in postnatal animals promotes neurogenesis by eliminating glucocorticoid production. Studies in animal models show that glucocorticoids act on mineralocorticoid (MR) and glucocorticoid receptors (GR), with GR primarily activated during stress, leading to downregulation of neurogenesis. GR affects both mature neurons and progenitors, while MR is only found on mature neurons, indicating that stress indirectly influences progenitor cells[21].

Serotonin and noradrenaline upregulate progenitor proliferation in the SGZ through antidepressants like TCAs, SSRIs, ECT, and MAOIs[22]. Damage to serotonergic neurons in the DG reduces SGZ neurogenesis, which can be restored by neuron implantation. The 5-HT1A receptor, a key regulator of neurogenesis, promotes cell proliferation in the hippocampus and SVZ. Mice lacking 5-HT1A showed no neurogenesis and were unresponsive to SSRIs, but responded to TCAs. Key findings include:

1. SVZ and SGZ respond differently to antidepressants,
2. SGZ neurogenesis is affected by stress and antidepressant treatment,
3. Stress impairs neurogenesis and behaviour, treatable by antidepressants,
4. Antidepressant effects depend on neurogenesis.

Neurogenesis in the SVZ, unlike the SGZ, is regulated by dopamine rather than SRIs or TCAs. Antipsychotic medications that lack 5-HT receptor affinity reduce SVZ neurogenesis, while those with affinity promote proliferation. Thus, serotonin and noradrenaline influence SGZ neurogenesis, while dopamine regulates it in the SVZ[23].

Depression is linked to hippocampal atrophy and reduced volume, as shown by magnetic resonance imaging (MRI). These changes may result from decreased cell proliferation in the dentate gyrus (DG) or increased neuronal apoptosis. Atrophy is also correlated with the duration of untreated depression and the frequency of episodes. Memory and

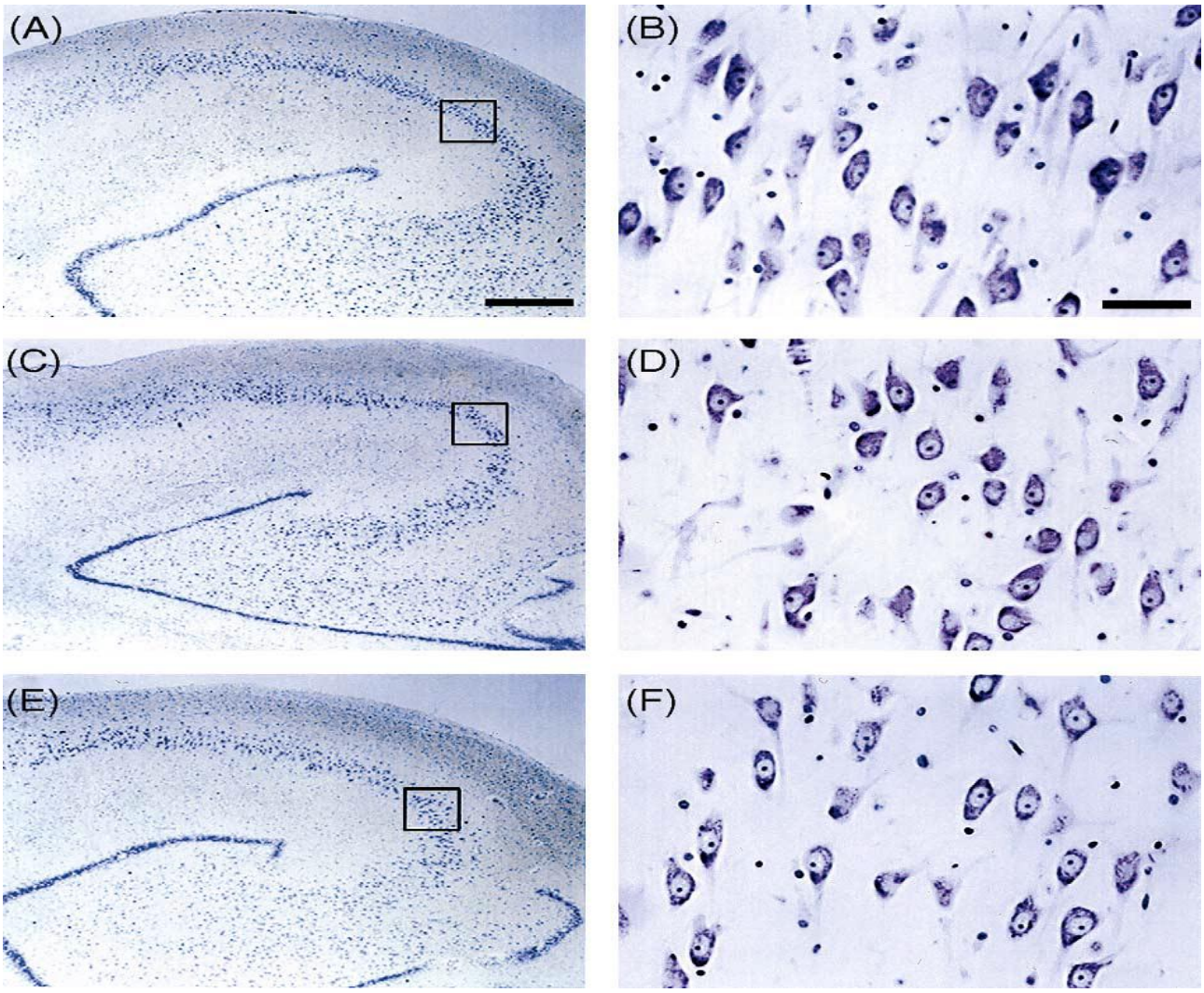

Figure 3. Photomicrographs of the hippocampus (left) and CA3 areas at higher magnification. A-B show a depressed patient, C-D a steroid-treated patient, and E-F a healthy control[20].

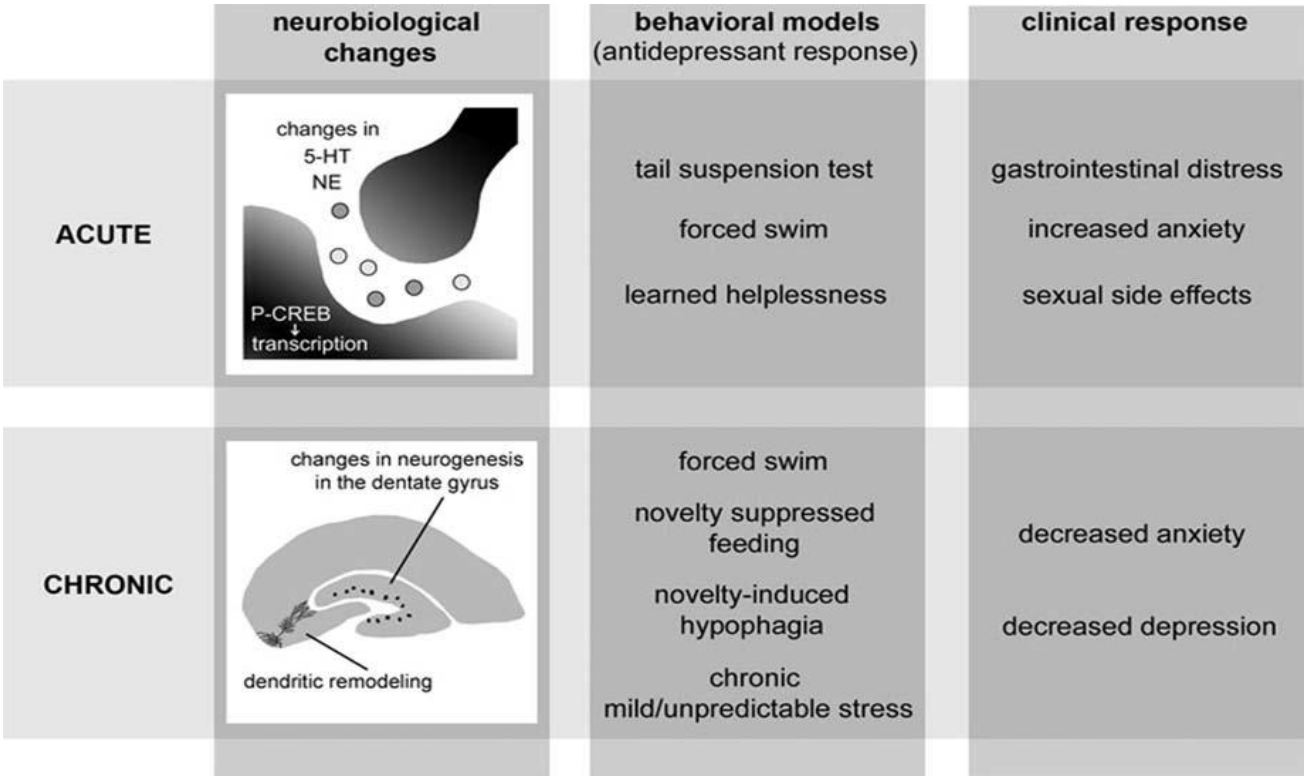

Figure 4. Effect of antidepressant treatment on acute and chronic response in the hippocampus. Chronic treatment promotes neurogenesis with hippocampal plasticity, however separate results are seen in behavioural models and clinical response[36].

learning impairments are often observed in depressed patients[24]. However, recent studies suggest that hippocampal volume changes are due to altered dendritic complexity and glial and neuronal numbers, rather than neurogenesis issues[25].

In response to depression, the hypothalamus releases corticotropin-releasing factor (CRF), stimulating the pituitary to produce adrenocorticotropic hormone (ACTH), which triggers glucocorticoid release from the adrenal glands. These hormones bind to hippocampal neurons, reducing neurogenesis and dendritic branching, while hippocampal inhibitory feedback regulates CRF release.

Studies using brain imaging show that, besides the hippocampus, depression affects the amygdala and prefrontal cortex. Stress contributes to hippocampal atrophy, while antidepressants can reverse the damage by restoring hippocampal plasticity. These findings indicate that both stress and depression directly affect hippocampal function and structure[26] (Figure 3).

Post-mortem research reveals increased neuronal and glial density in the DG of depressed patients, possibly contributing to reduced hippocampal volume. Volumetric changes were also observed in the hippocampus, amygdala, and prefrontal cortex, correlating with memory impairment[27].

Depression often co-occurs with substance misuse disorders. Elevated corticosteroid levels associated with stress can worsen hippocampal atrophy and inhibit DG cell proliferation. Animal studies suggest that neurogenesis impacts learning and memory, showing neurogenic activity's role beyond depression. Addiction and depression often follow cycles of relapse, with chronic psychological stress further exacerbating the condition[28].

Treating addiction and depression may involve increasing neurogenesis. Naltrexone, an opioid receptor blocker, has been shown to promote neurogenesis. However, antidepressants alone are not sufficient for addiction treatment, indicating multiple pathways influence neurogenesis. Ongoing research focuses on combining pharmacological and psychotherapeutic treatments and exploring advanced interventions, such as neural stem cell implants[29]. Neurogenesis is high during adolescence but decreases with age, leaving adults more susceptible to addiction. The prefrontal cortex plays a key role in determining addiction vulnerability.

The neurogenic interactome includes brain regions involved in neurogenesis, neurochemical, and endocrine signalling, impacting emotional stress and behaviour. This network helps explain why many antidepressants are independent of neurogenesis.

Different areas of the neurogenic interactome are activated when testing for depression, affecting stress levels, fear, and neurogenesis-dependent behaviour. Stress reduces neurogenesis, linking it to depression. Stress management is a natural antidepressant, comparable in effectiveness to chemical treatments.

While emotional disorders are linked to neurogenesis, more data is needed to understand whether brain regions involved in cell proliferation influence neurogenesis[30, 31].

Adult hippocampal neurogenesis is key to the therapeutic effects of antidepressants. Just as neuronal cell maturation in the SGZ takes weeks, antidepressants also need time to

exert their effects, highlighting the role of cell proliferation in treatment.

Drugs like noradrenaline (NA) and serotonin activate hippocampal receptors, regulating gene expression and inducing neuronal changes necessary for reversing depression and promoting cell proliferation. However, antidepressants do not affect the neuron-to-glia ratio[29].

Neurogenesis occurs in both the SGZ and SVZ, but antidepressant regulation varies between these regions, depending on drug properties. For example, 5-HT1A agonists stimulate hippocampal cell division, while antagonists inhibit it[25].

Animal studies show that neurogenesis is required for the behavioural effects of antidepressants, such as reducing stress and anxiety. Chronic antidepressant treatment is necessary for these effects, while acute treatments rely on synaptic function regulation. Results indicate that stress-related neurogenesis suppression is reversible with antidepressants[32].

Animal models are used to assess antidepressant responses to stress. While antidepressant treatments regulate 5-HT and NA levels, reducing treatment latency, some drawbacks include anxiety and nausea. Forced swim and tail suspension tests effectively measure antidepressant effects, particularly for chronic treatments[33] (Figure 4).

BDNF plays a role in adult neurogenesis, though its effects vary by brain region. In hippocampal areas, BDNF does not stimulate neurogenesis but affects cell survival and turnover in response to antidepressants[34].

Electroconvulsive therapy (ECT) is highly effective in severe depression cases, promoting neurogenesis by upregulating VEGF. VEGF aids antidepressant actions, increasing neurogenesis, while inhibiting VEGF blocks the proliferation effects of chemical antidepressants. VEGF is also crucial for the neurogenic effects of exercise, a natural antidepressant[35]. In conclusion, VEGF signalling is vital for both neurogenesis and neuron plasticity in antidepressant treatment.

Limitations

The review relies heavily on preclinical animal models, which may not fully capture the complexity of human depression. Additionally, the exact relationship between neurogenesis and the therapeutic effects of antidepressants is still debated, as neurogenesis-independent mechanisms may also contribute.

Conclusion

The neurogenesis hypothesis of depression suggests that reduced cell proliferation in the dentate gyrus (DG) is closely linked to the pathophysiology of depression, while an increase in this proliferation is crucial for the effectiveness of antidepressant treatments. However, depression cannot be induced solely by reducing neurogenesis. Similarly, decreases in hippocampal volume seen in depressed patients are not solely explained by reduced neurogenesis, as demonstrated by animal studies involving X-irradiation of mouse hippocampi, which showed no significant reduction in volume. Importantly, research confirms that neurogenesis is essential for antidepressant efficacy. Further studies may explore how to enhance neurogenesis in the DG to improve antidepressant outcomes.

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None.

Ethical consideration

Not applicable.

Competing Interests

The authors declare no conflict of interest.

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