ISSN 2959-6157

# Corticosterone-Mediated BDNF Changes and Their Effects on Adult Neurogenesis in Depression

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**Abstract:**

Adult neurogenesis, the process of generating functional neurons from neural precursor cells in the adult brain, is essential for cognitive function and emotional regulation. Major Depressive Disorder (MDD), characterized by persistent sadness and decreased psychosocial function, is associated with impaired adult hippocampal neurogenesis (AHN). Elevated levels of corticosterone (CORT), a glucocorticoid released in response to stress, have been shown to downregulate brain-derived neurotrophic factor (BDNF), a crucial regulator of neurogenesis, thereby inhibiting AHN. Despite significant advances in understanding the impact of CORT and BDNF on neurogenesis, the precise molecular and cellular pathways involved remain unclear. This review highlights key gaps in the research, particularly the need for a deeper understanding of how glucocorticoid and mineralocorticoid receptors regulate BDNF transcription, the role of autophagic pathways in BDNF degradation, and the influence of glutamatergic signaling on these processes. Future research should focus on elucidating these mechanisms to develop targeted therapeutic strategies, including pharmacological interventions that modulate BDNF and CORT levels and lifestyle modifications like exercise and adequate sleep to enhance neurogenesis. Understanding these complex interactions will be crucial for advancing treatments for depression and improving mental health outcomes.

**Keywords:** Corticosterone, BDNF, Adult neurogenesis, Depression

## 1. Introduction

Adult neurogenesis, the process by which functional neurons are generated from neural precursor cells in the adult brain, was first documented in the 1960s (1). However, this discovery, along with later evidence, faced significant skepticism in the scientific community due to the prevailing belief at the time that no neurons were generated postnatally (2, 3). Over time, numerous findings emerged in support of adult neurogenesis in various brain regions, such as the hippocampal dentate gyrus (DG), the subventricular zone (SVZ) of the olfactory bulb, and more recently, in the hypothalamus, amygdala, striatum, substanstia nigra, etc. (4). The process of adult hippocampal neurogenesis (AHN) begins with neural stem cell (NSC) proliferation and subsequent generation of neural progenitor cells (neuroblasts), which then migrate into the granular cell layer and mature into neurons. The exact pathways by which newborn neurons integrate into existing circuits are not understood, but it is known that integration involves intricate processes of dendritic and axonal growth, synaptic formation, and activity-dependent mechanisms (5).

Major Depressive Disorder (MDD) is characterized by persistent and intense feelings of sadness, despair, and hopelessness. Depressed individuals demonstrate decreased psychosocial function as well as diminished quality of life. Almost one in five individuals experience depressive episodes in their lifetime, marking the high prevalence of this neuropsychiatric disorder (6). Overactivity of the Hypothalamic Pituitary Adrenal (HPA) axis, which plays a key role in the body's response to stress, has been implicated to be involved in the pathophysiology of mental illnesses such as depression and schizophrenia. Stress-induced hypothalamic secretion of corticotropin-releasing hormone (CRH) stimulates the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH subsequently activates the adrenal cortex to release glucocorticoids, such as cortisol in humans and corticosterone (CORT) in rodents. The release of glucocorticoids inhibits CRH and ACTH secretion, creating a negative feedback loop (7). Research has shown that chronic stress exposure could impair adult neurogenesis and newborn cell survival in the DG area and cause depressive symptoms in MDD (8, 9).

Recent studies reveal that heightened corticosterone levels

enhanced autophagic flux and reduced brain-derived neurotrophic factor (10) levels in the brain (11). Given that BDNF is a regulator of neurogenesis, and antidepressant therapies restore BDNF levels, it could be inferred that stress-induced increases in CORT dysregulates BDNF levels, thereby inhibiting adult neurogenesis in the DG. That said, the specific cellular and molecular pathways by which CORT and BDNF interact to regulate AHN remain elusive. This review article aims to synthesize existing literature on the mechanisms by which CORT and BDNF influence adult neurogenesis and their implications for depression. By understanding these interactions, we can better inform the development of therapeutic interventions and improve mental health outcomes in the future.

## 2. BDNF Signaling Pathways in Adult Hippocampal Neurogenesis

Brain-derived neurotrophic factor (10) is a neuropeptide of the neutrophin family. There is an abundance of evidence reporting BDNF's participation in numerous cell signaling pathways, as well as its role in neuronal development, synaptic plasticity, and its importance for the efficacy of neuropsychiatric therapies (12). Following synthesis and protein folding in the endoplasmic reticulum, preproBDNF is translocated to the Golgi apparatus and undergoes multiple rounds of proteolytic cleavage. This process forms proBDNF, which then matures into its active form, mBDNF. Both proBDNF and mBDNF can diffuse cross the blood-brain barrier (BBB) and exert their effects by binding to specific receptors: proBDNF binds to the p75 neurotrophin receptor (p75NTR), while mBDNF binds to the tropomyosin receptor kinase receptor (TrkB). Activation of TrkB by mBDNF initiates dimerization and autophosphorylation of the tyrosine residue, activating enzymes that trigger downstream signaling cascades, such as MAPK/ERK, PI3K/Akt, and PLC-γ-dependent pathways (13).

Both TrkB and p75NTR are involved in adult neurogenesis, but they play different roles in this process. For instance, TrkB is responsible for promoting hippocampal LTP and NSC proliferation in the DG. Additionally, exercise enhances BDNF-TrkB pathways, inhibiting apoptosis in the diabetic cerebral cortex. Hence, BDNF signaling via the TrkB likely mediates neuroprotective events and promotes neuronal survival (14). On the other hand, deletion of p75NTR does not affect cell proliferation in adult mice, suggesting that the receptor does not directly influence NSC proliferation (15). Instead, p75NTR mediates apoptosis and axonal regeneration. Moreover, p75NTR can act as a co-receptor for TrkB, increasing TrkB's ligand selectivity. Based on the findings above, it appears that pro-forms of BDNF preferentially activate p75NTR to modulate apoptosis whereas mature forms target TrkB to mediate survival. Overall, the effects of p75NTR and TrkB appear to be complementary and context-dependent (16).

Past studies show the importance of BDNF in environmental enrichment-induced adult neurogenesis and the effects of its reduction in suppressing newborn cell proliferation (17). In addition, blockade of early postnatal BDNF-TrkB signaling during early life stress exposure exacerbated depressive behavior. Stress also reduced BDNF levels to a greater extent in TrkB knockdown mice, when compared to controls (18). Given that depression is associated with decreased adult neurogenesis, a link could be drawn between BDNF-TrkB signaling and adult neurogenesis, in that a reduction in BDNF or TrkB levels could reduce newborn cell differentiation. However, much controversy surrounds the role of TrkB receptors in cell differentiation. For example, (Groves et al., 2019) demonstrated that TrkB stimulation had no effect on neurosphere assays, wheareas TrkB blockade directly activates a subpopulation of quiescent neural progenitor cells (NPCs) and enhances AHN (19).

BDNF signaling also phosphorylates cAMP response element-binding protein (CREB), a transcription factor that regulates the expression of genes involved in neuronal plasticity. Hence, BDNF signaling pathways not only promote neuronal proliferation, survival, but also long-lasting potentiation (L-LTP) and long-term memory (LTM) (10). Unsurprisingly, downregulation of BDNF expression or TrkB receptor inhibition impaired spatial memory while BDNF upregulation restored cognitive deficits in early-life stress (ELS) models, highlighting the role of BDNF-TrkB pathways in cognition (20).

## 3. Corticosterone-Induced Changes in BDNF and Adult Hippocampal Neurogenesis

Corticosterone (CORT), the rodent equivalent of cortisol in humans, plays a significant role in the stress response and has been extensively studied for its impact on brain function and structure. Research form the late 20th century has already discerned the effect or CORT on downregulating BDNF mRNA and protein in the rat hippocampus (21). In this section, we will delve deeper into the effect of CORT on BDNF and its implications for AHN.

### 3.1 Corticosterone Regulation of BDNF Expression and Protein Levels

Corticosterone regulates BDNF expression at multiple levels, beginning with transcription. The glucocorticoid receptors (GR) and mineralocorticoid receptors (MR)

function as transcription factors, when activated by CORT, directly binds to the promoter region and regulates BDNF expression. The exact role of each receptor, or whether both are responsible for the downregulation of BDNF mRNA in the hippocampal region, remains unclear. However, it has been proposed that MRs are primarily responsible for suppressing mRNA expression in the Cornu Ammonis (CA) regions, while GRs predominantly affect the dentate gyrus (DG) (22). Different doses of CORT also exert varying effects on BDNF mRNA levels in the brain, possibly due to differences in receptor affinity for the molecule. Specifically, MRs have a higher affinity for corticosterone and are activated at lower concentrations, whereas GRs are activated at higher concentrations of the hormone, leading to distinct regulatory outcomes (22).

Additionally, GRs interact with other transcription factors, such as cAMP response element-binding protein (CREB), which also binds to the BDNF promoter and can either enhance or repress BDNF transcription depending on the cellular context and the presence of specific co-factors (Koo et al., 2019). Thus, complex mechnisms of multiple receptors, signaling pathways, and regulatory elements converge to transcriptonally control BDNF expression in response to stress and glucocorticoid signaling.

Beyond transcriptional regulation, CORT affects the translation of BDNF mRNA. For instance, CORT reduced BDNF protein expresson in the prefrontal cortex, whereas protein expression was unchanged in the hippocampus. Reduced levels of BDNF these brain regions are related to atrophy and cell loss and are commonly found in depressed patients (23).

In a corticosterone-induced mouse model of depression, there is an increase in astrocyte and microglia neuronal autophagy, along with lysosomal degradation of BDNF in the hippocampus. However, it remains unclear whether this autophagy specifically targets BDNF mRNA or the BDNF-producing Golgi apparatus and endoplasmic reticulum. Generally, CORT induces hyperactive neuronal autophagy, leading to reduced BDNF mRNA and protein levels (11). There also seems to be distinct autophagic signaling pathways that promote cell death and survival; 2-deoxy-D-glucose (2DG) induce cytoprotective autophagy whereas Glycogen synthase kinase-3 beta (GSK-3β) mediates death-inducing autophagy (24). Thus, cell death and survial are likely differentially regulated, but it unclear whether autophagy by the GSK-3β pathway depletes BDNF or cause depressive phenotypes.

Localized protein synthesis is critical for synaptic plasticity, neural growth, and survival. Chronic mild stress has been shown to reduce BDNF trafficking in dendrites, making less BDNF mRNA is available in the for translation into BDNF protein, leading to decreased localized BDNF levels. It has also been shown that certain compounds (ketamine) achieve antidepressant effects through improving BDNF dendritic trafficking instead of restoring BDNF mRNA directly. However, these phenotypes are only observed in stress-vulnerable rats (25).

Overall, CORT exerts multi-faceted effects on transcription, translation, and cell dynamics to downreglate BDNF levels in the brain.

## 3.2 Impact of Corticosterone-reduced BDNF on Adult Hippocampal Neurogenesis

Glucocorticoids, after synthesis, generally diffuse across the blood-brain barrier and bind to glucocorticoid or mineralocorticoid receptors. This interaction facilitates their modulation of transcriptional and translational processes, influencing the expression of genes involved in various cellular functions, including adult neurogenesis.

Chronic mild stress reduced BDNF mRNA dendritic trafficking in CA1 and CA3 hippocampal regions (25). Similarly, chronic CORT administration was shown to suppress AHN via decreased BDNF vesicular transport from hungtington hyperphosphorylation by CDK5. Conversely, an unphosphorylatable form of huntington protects against the depressive effects of CORT on AHN (26).

Past studies show that glucocorticoid receptors (GRs) interact with TrkB for BDNF, that chronic CORT treatment decreased TrkB-GR interaction and suppressed BDNF-mediated glutamate release via suppression of BDNF-activated PLC-γ (phospholipase C-γ)/ $Ca^{2+}$ signaling pathways (27). We know that DG neurons receive excitatory input from glutamate via the entorhinal pathway and that cultured hippocampal NPCs respond to glutamate by increasing neuronal proliferation (28). Recent literature reveals the importance of N-methyl-D-aspartate (NMDA), a glutamatergic receptor, in the normal development of the DG, where NMDA knockout reduced neural proliferation, impaired newborn granule cell survival, and decreased GCL volume (29).

Given the available research, it appears that glutamate plays a crucial role in cell signaling pathways from chronic CORT exposure to adult neurogenesis and the subsequent development of newborn neurons. In addition, a 2014 study utilizing a human GFAP promoter-driven thymidine kinase genetic mouse model to suppress adult neurogenesis reveals that chronic ablation of newborn neurons induces CA3 neuron remodeling and increases stress-induced release of glutamate. Moreover, it showed that, in response to acute stress, the HPA axis was mildy hyperactive following the ablation of neurogenesis (30). As previously mentioned, chronic HPA axis disruption alters glutamatergic signaling in hippocampal regions, providing more evidence linking HPA dysfunction and stress

vulnerability (31). However, it also further muddies the waters regarding the role of glutamate in CORT regulation of BDNF-induced AHN. This suggests a complex interplay between adult neurogenesis, glutamatergic signaling, and stress response mechanisms within the hippocampal circuitry. The observed alterations in CA3 highlight the significance of adult neurogenesis in maintaining hippocampal integrity and function, implicating glutamate as a key mediator in these processes under conditions of impaired neurogenic activity. Further research is warranted to elucidate the precise mechanisms through which these effects occur and their implications for AHN.

CORT-induced BDNF autophagy is also shown to be related to depressive symptoms in mice. Inhibiting autophagy enhanced BDNF expression, NSC and neuroblast survival and proliferation, newborn neuron survival, and improved performance across a myriad of behavorial tests for depression (11). Research on stress-mediated autophagy is highly heterogeneous, with a variety of adopted experimental protocols. Hence, signaling pathways involveing mTOR, AMPK, PI3K/Akt, and MAPK are all implicated across various studies (32).

Overall, the intricate relationship between corticosterone, BDNF, and adult hippocampal neurogenesis underscores the pivotal role of glutamate signaling in mediating these effects. Further exploration of these mechanisms is crucial for a deeper understanding of stress-related disorders and potential therapeutic interventions targeting neurogenesis and glutamatergic signaling pathways.

## 4. Clinical Implications and Therapeutic Strategies

Simply increasing adult neurogenesis is sufficient to reduce anxiety and depressive-like behaviors in rodents (33). Hence, adult neurogenesis has been of particular interest in developing therapeutic strategies for psychiatric disorders, including MDD.

In the quest to develop effective treatments, understanding the underlying mechanisms of adult neurogenesis and its regulation by factors such as BDNF and corticosterone is crucial. This section highlights the clinical implications of these findings and explore potential therapeutic strategies that leverage existing knowledge.

Classical antidepressants, such as tranylcypromine, fluoxetine, and reboxetine, increase cell proliferation. Evidence has also revealed the mechanistic dependence of antidepressants on adult neurogenesis. For instance, the 2 week lag in antidepressant-induced neurogenesis is consistent with the temporal delay in antidepressant efficacy. Conversely, blocking neurogenesis has been shown to prevent antidepressant effects (34, 35).

In addition, rewarding experiences, such as physical exercise and environmental enrichment (EE) can reduce depressive symptoms in MDD as well as improve cognitive function and reduce amyloid load in Alzheimer's disease (AD) patients. Interestingly, AHN activation is required for these exercise-induced improvements in memory, and that inducing AHN in combination with BDNF mimicked the effects of exercise on AD mice. This has implications for both lifestyle changes and therapeutic intervention for cognitive deficits, a major hallmark for depression (36). On one hand, exercising-induced adult neurogenesis could be beneficial for managing symptoms. On the other hand, stimulating cell proliferation via BDNF achieves similar effects. However, the combinatorial effects of physiotherapy and BDNF enhancement remains elusive and is an area of research for therapeutic development.

Given that sleep deprivation inhibits adult hippocampal neurogenesis by elevating glucocorticoids such as cortisol, maintaining sufficient sleep is crucial for psychological well-being (37). Notably, recovery from sleep deprivation requires approximately two weeks, mirroring the time needed for neurogenesis rates to rebound and for antidepressant effects to become evident. These findings suggest that preventing stress and regulating stress-related molecules could serve as effective strategies for therapeutic development.

Additionally, recent literature has shown that activating newborn neurons suppress anxiety and depressive behavior. Stimulation of these neurons is also necessary for fluoxetine's antidepressant effects (38). This shows the importance of not only neurogenesis but also activation of newly generated cells in alleviating depressive phenotypes.

Overall, research of the role of adult neurogenesis has allowed us to develop a comprehensive understanding of depression and explore plausible therapeutic strategies.

## 5. Conclusion

Findings from the late 20th century on serotonin's role in increasing adult neurogenesis have led to hypotheses about reduced neurogenesis contributing to early depressive episodes and chronic depressive states, with its restoration aiding in recovery. Over time, studies have largely supported these conjectures. Research into the effects of corticosterone and BDNF on adult neurogenesis has further elucidated the intricate mechanisms underlying depression. The suppression of neurogenesis by elevated corticosterone and the regulation of this process by BDNF highlight critical pathways that can be targeted for therapeutic interventions. Understanding these interactions not only informs the development of pharmacological treat-

ments but also underscores the importance of lifestyle factors, such as exercise and sufficient sleep, in maintaining psychological well-being. Continued exploration of these mechanisms is essential for developing comprehensive and effective treatment strategies for depression, leveraging both pharmaceutical and lifestyle interventions to enhance neurogenesis and improve mental health outcomes.

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