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Glucocorticoid-Mediated Regulation of BDNF and Autophagy in Dentate Gyrus Neurons

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Abstract. Chronic stress is an important risk factor for depression and is associated with sutained glucocorticoid signaling and impaired hippocampal function. Prolonged exposure to corticosterone, a major glucocorticoid, can distrpt adult hippocampal neurogenesis (AHN) in the dentate gyrus (DG) and reduce brain-derived neurotrophic factor (BDNF), which contributes to the differentiation and maturation of adult-born neurons through TrkB signaling. This review focuses on the studies showing that chronic CORT exposure increases neuronal autophagy in the DG and reduces BDNF levels, and disccus the current evidence linking CORT-induced neural autophagy to BDNF loss. While inhibition of autophagy can restore BDNF and partially rescue impaired AHN, whether GR mediates CORT-induced autophagy in DG neurons remain unanswered. In addition, GR signaling may influence BDNF through autophagy-independent mechanisms, including direct regulation of BDNF transcription. Together, the current studies supports a potential model in which GR-mediated autophay coontributes to intracellular BDNF loss following chornic CORT. This propsoed mechanism provides a direction for further examing how prolonged glucocorticoid signaling participates in impaired AHN.

Keywords: adult hippocampal neurogenesis, glucocorticoids, autophagy, BDNF, dentate gyrus

1. Introduction

In decades, many studies have indicated that chronic stress plays an important role in the dysfunction of hippocampus. Chronic stress can produce sustained effects on hypothalamic-pituitary-adrenal axis (HPA axis) and glucocorticoid signaling. The hippocampus is one of the brain regions most sensitive to glucocorticoids (GCs) due to its high density of glucocorticoid receptors (GRs) and contains corticosteroid receptors that mediate the effects of adrenal stress hormones [1]. Although glucocorticoid signaling is involved in the normal physiological response to stress, prolonged exposure to elevated glucocorticoid levels can alter hippocampal neuronal structure, synaptic plasticity, and hippocampus dependent functions [1, 2]. Within the hippocampus, the dentate gyrus (DG) undergoes adult hippocampal neurogenesis (AHN), a process in which neural stem cells can generate new neurons even during the adulthood. During AHN, neural stem and progenitor cells proliferate and differentiate into new DG neurons that become a part of hippocampal circuits [3, 4]. This process is sensitive to stress and glucocorticoid exposure [4, 5].

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High concentration of corticosterone (CORT) can suppress DG cell proliferation and damage AHN [6, 7].

The brain-derived neurotrophic factor (BDNF) is an important neurotrophic factor involved in the development of adult-born neurons [8, 9]. BDNF binds to tropomyosin receptor kinase B (TrkB) and activates downstream signaling cascades. Chronic CORT exposure can reduce hippocampal BDNF levels and decrease BDNF expression in DG neurons [7]. A recent study further suggests that autophagy is involved in CORT-related BDNF loss [7]. However, the molecular mechanism of upstream for CORT-induced neuronal autophagy in the DG remains unclear. Meanwhile, glucocorticoid treatment has been shown to increase REDD1 expression, suppress mTOR signaling, and alter autophagy-related markers in mouse epidermis [10]. This review focuses on the potential role of GR-dependent autophagy in linking CORT exposure to changes in intracellular BDNF within DG neurons and analyze whether this potential mechanism may be cell-autonomous. A better understanding of this pathway may offer further insight into the molecular mechanisms through which chronic stress contributes to depression-related hippocampal dysfunction.

2. Corticosterone and hippocampal dysfunction

2.1. Chronic stress and glucocorticoid signaling

Chronic stress engages in neuroendocrine responses, with glucocorticoid signaling through the hypothalamic-pituitary-adrenal (HPA) axis playing an important mediator in stress-induced effects on the hippocampus [1]. The hippocampus is particularly responsive to glucocorticoids because it contains abundant corticosteroid receptors, which participates in glucocorticoid-mediated negative feedback of the HPA axis [1]. In rodents, corticosterone (CORT) is the major glucocorticoid. It acts through mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) in hippocampus [1].

The effects of glucocorticoids on the hippocampus vary with the magnitude and duration of exposure [1, 2]. Glucocorticoid signaling usually forms part of the normal physiological response to stress, but prolonged elevation of glucocorticoids can alter hippocampal neuronal morphology, synaptic plasticity, and hippocampus-dependent cognitive function [1, 2]. Chronic CORT treatment in rodents has been reported to suppress cell proliferation within the dentate gyrus [4, 5].

2.2. Effects of CORT on the dentate gyrus

The DG is unusual among regions of the adult mammalian brain because it continues to generate neurons throughout adulthood [3]. This ongoing generation of new dentate granule neurons has been linked to the regulation of hippocampal circuit function and behavior [3, 4]. AHN therefore represents a cellular process through which stress-related signaling can influence DG function [4]. Glucocorticoids are known to regulate this neurogenic process. Glucocorticoids released by the adrenal glands in response to stress can influence AHN by altering the proliferation and differentiation of neural stem and progenitor cells [5]. Moreover, direct injection of CORT in adult rats is sufficient to reduce neurogenesis in the DG [6]. Thus, chronic stress may disrupt neurogenesis through glucocorticoid signaling in the DG [5]. More recent study indicates that the effects of chronic CORT extend across multiple stage of the adult neurogenic process. According to Zhang et al., chronic CORT exposure reduced proliferation of neural stem cells, neural progenitor cells, and neuroblasts in the DG. In addition, chronic CORT exposure was associated with a loss of neuronal BDNF expression within the DG [7]. These findings indicate that CORT-induced disruption of the DG involves both impaired AHN and molecular changes within hippocampal neurons [7].

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3. BDNF signaling in the dentate gyrus

3.1. BDNF and adult hippocampal neurogenesis

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family and is involved in neuronal development in the central nervous system [8]. BDNF signaling has also been implicated in AHN, including several stages of newborn neuron development and maturation [8, 9]. Adult-born dentate granule cells (DGCs) express BDNF, and BDNF derived from these cells regulate their development through an autocrine mechanism [8]. BDNF overexpression promoted dendritic growth in these cells [8]. Thus, BDNF involved in the maturation of newborn DG neurons can originate from the newborn neurons themselves [8].

3.2. BDNF/ TrkB signaling

Many of the effects of BDNF on adult-born neurons are mediated through TrkB [11]. TrkB is encoded by the NTRK2 gene and belongs to the tropomyosin receptor kinase family of neurotrophin receptors. BDNF binds to TrkB and activates intracellular signaling cascades invovled in the neuronal differentiation of progenitor cells [11]. TrkB signaling also plays a role in the later maturation and integration of newly generated dentate granule cells into hippocampal circuits [11]. Therefore, changes in BDNF may alter TrkB signaling and thereby affect the development and maturation of adult-born neurons in the DG [11].

3.3. Effects of CORT on BDNF

In a C57BL/6 mouse model, chronic CORT exposure significantly reduced hippocampal BDNF protein levels [12]. The other study focused on changes in neuronal BDNF in the DG. Following 8 weeks of continuous CORT exposure, both BDNF protein and BDNF mRNA levels in the mouse DG were significantly reduced [7].

Besides being produced locally by DG neurons, BDNF can also reach the hippocampus through another pathway from the entorhinal cortex (EC). In this process, BDNF is packaged into BDNF-containing vesicles and undergoes anterograde axonal transport along cortical axons toward hippocampal targets [13]. The overactivation of cyclin-dependent kinase 5 (CDK5) increases the phosphorylation of huntingtin (HTT) at the S1181 and S1201 sites and reduces both the anterograde transport velocity and net flux of BDNF-containing vesicles [13]. A vivo experiments showed that chronic CORT exposure induces CDK5/p25 signaling and HTT phosphorylation and finally reduced hippocampal mature BDNF levels [13]. Beyond the regulation of BDNF axonal transport, studies have also examined neuronal autophagy as a potential pathway for BDNF degradation.

4. Autophagy in CORT – induced hippocampal dysfunction

4.1. Neuronal autopahgy

Autophagy is an important degradative mechanism in neurons that removes damaged organelles and proteins through lysosomal degradation and recycling [14]. During macroautophagy, portions of the cyctoplasm, including proteins or organeles, are encolsoed bydouble-membrane sutrcutres to form autohphagosomes. These autophagosomes subsequentely fuse with endosomal or lysomal degradative compartents, where the enclosed intracellular materials are degraded [14]. GFP-LC3 and live cell imaging showd that many LC3-positive autophagosomes formed in distal axons and

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moved toward the cell soma through retrograde transport [15]. The autophagosomes acquried late endosomal or lysosomal markers such as LAMP1 during the transport [15].

4.2. CORT-induced autophagy

Over the past few years, chronic stress and sustained elevation of CORT have been proved to affect autophagic activity in the hippocampus. ATG7 (autophagy-related protein 7) is an E1-like enzyme required for autophagosome formation [16]. Atg7 knockout was used to examine the hippocampal changes induced by autophagy [16]. Jung et al. used chronic restraint stress (CRS) mouse model and found that chornic stress significantly reduced the number of adult hippocampal neural stem cells (NSCs) and suppressed AHN in mice with normal Atg7 expression [16]. In contrast, the mice with Atg7 knockout showed significantly less impairment of AHN and NSC loss.

Jung et al. also treated cultured adult hippocampal NSCs with CORT and found that CORT exposure increased autophagic activity and induced autophagy-dependent cell death, while inhibition of key autophagy genes significantly reduced this cell death [16]. However, this study did not directly investigate CORT-induced autophagy in DG neurons. More recently, this question has been addressed in a chronic CORT mouse model. Neuronal autophagy in the DG increased significantly following CORT exposure with increase in both autophagosomes and autolysosomes [7]. Moreover, neuronal Atg5 knockdown restored neuronal BDNF levels in the DG following chronic CORT exposure, supporting a contribution of neuronal autophagy to CORT-induced BDNF loss [7].

5. Glucocorticoid receptor signaling and autophagy

5.1. GR signaling in the hippocampus

Glucocorticoid (GC) exert many of its effects on the brain through the glucocorticoid receptors (GRs). GR is widely involved in the regulation of stress responses [17]. The hippocampus cotntains abundant mineralocorticoid receptors (MRs) and GRs, but these two receotpros have different affinities for endogenous glucocorticoids. MR has a higher affinitiy, whereas GR has a lower affinity. When glucocorticoid levels increase, the effect of GR signaling becomes more prominent [17, 18].

After glucocorticoids binds to GR, GR affects cellular functions through both genomic and non-genomic mechanisms, and eventually convers the changes into intracellular molecular responses [17]. In the genomic mechanism, activated GR acts as a transcriptional regulator influencing the expression of target genes; while in non-genomic mechanisms, GR interact with intracellular signaling pathways to regulate neuronal function [17]. In cultured human hippocampal progenitor cells, Anacker et al. found that high concentrations of cortisol, a type of GC, increase GR transcriptional activity and subsequently reducing cell proliferation and neuronal differentiation [18]. When the researchers used the GR antagonist RU486 to block GR, the effects of high-concentration cortisol on cell proliferation and neuronal differentiation were inhibited. To ensure the effects were mediated by GR, the researchers used GR agonist dexamethasone (DEX) to activate GR. The result showed that DEX mimicked some of the cellular effects produced by high-concentration cortisol [18]. These experiments together suggest that elevated GC levels can induce cellular and molecular changes in hippocampal cells through GR-mediated mechanisms [18].

Data from rat hippocampus demonstrated the effects of GR during memory formation were associated with CaMKIIα and BDNF-related TrkB, ERK, Akt, PLCγ, and CREB signaling activities

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[19]. Blocking GR disrupted these molecular signals and memory consolidation [19]. Furthermore, administration of BDNF in the hippocampus was able to restore some of the molecular signaling deficits and memory impairments caused by GR inhibition, further supporting a functional relationship between GR and BDNF-related neuronal signaling [19].

5.2. GR regulation of autophagy

Shimizu et al. identified REDD1 as a direct transcriptional target of GR in skeletal muscle [20]. DEX increased REDD1 expression. Importantly, GR knockdown diminished DEX-dependent REDD1 induction [20]. The researchers then identified a functional glucocorticoid response element (GRE) in the REDD1 promoter [20]. They detected DEX-dependent recruitment of GR to this region [20]. REDD1 can inhibit mTOR activity, and DEX treatment suppressed the phosphorylation of the downstream mTOR targets S6K1 and 4E-BP1 in skeletal muscle [20]. These results connect GR-dependent transcription with REDD1 induction, mTOR suppression, and changes in autophagy-related gene expression [20].

In another study, Baida et al. found that glucocorticoid treatment increased expression of REDD1, an inhibitor of mTOR, and inhibited mTOR activity in skin [10]. Topical treatment with the glucocorticoid fluocinolone acetonide increased REDD1 mRNA and protein expression [10]. As result, mTOR activity was suppressed and reduced the phosphorylation of its downstream targets, 4E-BP1 and rpS6 [10]. In the same model, glucocorticoid treatment increased LC3-I to LC3-II conversion and Beclin-1 expression. This change indicated increased autophagy-related activity [10]. These results support a pathway linking glucocorticoid-induced REDD1/mTOR regulation with autophagy, as shown in Figure 1 [10, 20]. These studies suggest that GR signaling is associated with autophagy, and that glucocorticoid exposure can activate autophagy-related pathways involving REDD1/mTOR. However, the specific involvement of GR in CORT-induced autophagy in DG neurons has not been directly demonstrated.

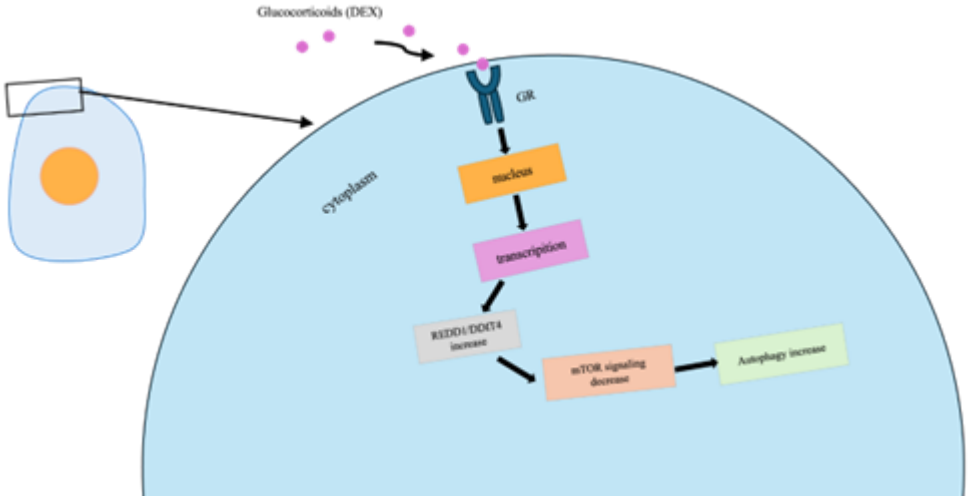


Figure 1. REDD1/mTOR signaling in glucocorticoid-induced autophagy

DEX, a synthetic glucocorticoid, crosses the cell membrane and binds to the GR. Activated GR then enters the nucleus and regulates transcription. In the nucleus, activated GR regulates gene transcription by binding to glucocorticoid response elements (GREs) [20]. REDD1/DDIT4 functions as an inhibitor of mTOR signaling, reducing mTOR signaling [10]. Because mTOR normally suppresses autophagy, reduced mTOR activity favors autophagy [10, 20]. Baida et al. observed

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increased LC3-I to LC3-II conversion and increased Becling-1expression following glucocorticoid treatment, which occurred with high REDD1 expression and strong mTOR repression [10]. Arrows indicate the direction of proposed signaling pathway.

5.3. Potential relationship between GR and CORT-induced neuronal autophagy

So far, the available findings indicate a possible mechanistic relationship between chronic CORT exposure, GR signaling, and neuronal autophagy. However, no experiments directly support a GR-dependent pathway linking CORT-induced autophagy to intracellular BDNF changes in DG neurons. It also remains unclear whether this GR-dependent effect occurs within DG neurons or is indirectly mediated by intercellular signals from other cells [7, 18].

Even if experiments confirm a GR-dependent reduction in BDNF after CORT exposure, autophagy does not necessarily account for the entire effect. Chen H et al. found that activation of GR with the GR agonist DEX reduced BDNF mRNA expression in neuron -like cells and primary neuronal cultures [21]. In contrast, the GR antagonist RU486 prevented this reduction [21]. In the same study, the research detected that GR was recruited to a regulatory region associated with BDNF exon IV, supporting a direct role for GR in the transcriptional regulation of BDNF [21]. Thus, GR signaling may also influence BDNF through a pathway independent of autophagic degradation by directly regulating Bdnf gene expression [21].

6. Discussion

Current studies support that chronic CORT exposure is increases neuronal autophagy, reduces BDNF levels, and impairs AHN in the DG. In mice exposed to chronic CORT, neuronal autophagy in the DG was significantly increased. At the same time, neuronal BDNF levels and several stages of AHN were reduced [7]. More importantly, inhibition of neuronal autophagy restored BDNF levels with partially rescued deficits in neurogenesis [7]. Therefore, autophagy may represent a molecular mechanism by which chronic COT exposure reduces intracellular BDNF in DG neurons.

Other studies also implicated GR as upstream of this autophagic response. Glucocorticoids can induce cellular changes in hippocampal-derived cells through GR-dependent mechanisms [18]. Moreover, glucocorticoid exposure promotes autophagy through REDD1/mTOR signaling in other cell type [10, 20]. These findings point to a possible role of GR as an upstream regulator or CORT-induced neural autophagy. A potential pathway can be therefore proposed in which chronic CORT exposure activates GR-dependent mechanisms, leading to increased neuronal autophagy and subsequent reduction of intracellular BDNF.

The reduction of BDNF contributes to impaired AHN. BDNF and TrkB signaling participate in the differentiation and maturation of adult-born neurons in the DG [8, 11]. Accordingly, increased autophagy reduces BDNF levels and consequently limits the available BDNF required for the development of adult-born neurons. However, several questions about this proposed pathway remain unanswered. For example, GR may influence BDNF through other mechanisms rather than autophagy, such as direct regulation of BDNF transcription. In addition, no study has directly demonstrated that GR is required for CORT-induced autophagy in DG neurons. Future studies could directly manipulate GR in CORT-treated DG neurons and examine the role of Akt/mTOR signaling, which may help identify the molecular mechanisms.

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7. Conclusion

Chronic CORT exposure may increase neuronal autophagy through GR-dependent mechanisms, leading to reduced intracellular BDNF and impaired AHN in the DG. The findings summarized in this review suggest that a pathway underlying CORT, GR, neuronal autophagy, BDNF, and AHN. Considering these processes provide a broader explanation for how changes in glucocorticoid signaling affect molecular regulation within DG neurons. Understanding this potential pathway may clarify the regulation of intracellular BDNF under chronic CORT exposure and its role in AHN.

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