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Review Article

Role of BDNF-TrkB Signaling in Regulating Anxiety and Depression-Like Behavior in Diverse Brain Regions

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Abstract: Depressive disorders occur often jointly with anxiety disorders, which can cause serious health problems. The underlying mechanism is not fully understood. Figuring out the mechanism of depressive and anxiety disorders would benefit patients in future therapy. Brain-derived neurotrophic factor (BDNF) is a famous neurotrophin that modulates synaptic plasticity in the brain. It is generally believed that decreased BDNF levels are associated with depression. The purpose of this review is to elucidate the role of the BDNF-TrkB signaling pathway in different brain regions and its antidepressant effect, to provide scientific evidence for the treatment of anxiety and depression. The changes of the BDNF-TrkB signaling pathway before and after antidepressant treatment were compared by retrieving preclinical studies related to the BDNF-TrkB signaling pathway and classifying them according to different brain regions. It is found that the concentration of BDNF varies in different brain regions. The inhibition of the BDNF-TrkB pathway in the cortex, hippocampus, and amygdala and the activation of the BDNF-TrkB pathway in the anterior cingulate cortex (ACC), nucleus accumbens (NAc), and lateral habenula (LHb) is associated with anxiety and depression-like behaviors. Lacking BDNF or its receptor TrkB is not the cause of anxiety or depression, but affects the effect of antidepressant treatment. Increased BDNF can alleviate anxiety and depression. There are still other molecules that can regulate anxiety and depression-like behaviors by influencing the expression of BDNF or TrkB. The function of BDNF in the ACC, NAc, and LHb areas needs to be further explored.

Keywords: Depression, Anxiety, BDNF, TrkB, Mechanism, Pathway

1. Introduction

Depressive disorders are mental disorders characterized by the presence of a sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function [1]. Depressive disorders occur often jointly with anxiety disorders [2]. Around 85% of patients who have depression will also exhibit symptoms of anxiety, while up to 90% of individuals with anxiety disorders will also experience comorbid depression [3]. Depression and anxiety were two of the top ten causes of global disability-adjusted life-years (DALYs) in adolescents aged 10–24 years in 2019 [4]. About 4.7% of the world's population has an episode of depression every year [5]. The causes of depression and anxiety disorders are complex, including genetic factors and environmental factors. People with high depression polygenic risk scores [6] are more susceptible to depressive disorders. Adverse experiences such as social isolation [7], trauma [6], and childhood maltreatment [8] were significantly associated with depressive disorders. During the pandemic of COVID-19, the global prevalence of major depressive disorders (MDD) and anxiety disorders increased [9]. Figuring out the underlying mechanism is important to treat these mental disorders effectively. The pathogenesis of depressive disorders is not fully understood. There are some hypotheses about depression, including the neurotrophic hypothesis, monoamine hypothesis, hypothalamic-pituitary-adrenal axis hypothesis, etc. [10].

Brain-derived neurotrophic factor (BDNF), which is widely expressed in the brain, is the most studied neurotrophic factor

and plays a key role in the central nervous system by supporting neuron survival and facilitating neurogenesis [11]. It performs biological functions by binding to its specific receptors. There are at least two BDNF-specific receptors, TrkB and $P75^{NTR}$, on the nerve cell membrane, and BDNF has a higher affinity with TrkB. Cavaleri D et al. found that people with MDD have lower peripheral and central BDNF levels than non-depressive individuals, based on meta-analyses [12].

To explore the molecular mechanisms of depression and anxiety and the effect of antidepressant treatment, experimental paradigms such as chronic unpredictable mild stress (CUMS), chronic restraint stress (CRS), learned helplessness (LH), corticosterone (CORT), lipopolysaccharide (LPS), etc. were used to induce animals showing anxiety and depression-like behaviors. In this review, we will elucidate the function of the BDNF-TrkB signaling pathway in diverse brain regions by giving a summary of the preclinical anxiety and depression-like behaviors studies.

2. BDNF-TrkB Signaling Pathway in Anxiety and Depression-Like Behavior

Impaired BDNF-TrkB signaling is associated with anxiety and depression-like behaviors (Figure 1). BDNF levels in MDD patients changed before and after antidepressant treatment. The studies on MDD patients' post-mortem brain samples found that the levels of BDNF were decreased in the hippocampus [13] and amygdala [14]. After the effective treatment of antidepressant drugs [15] or electroconvulsive therapy (ECT) [16], the serum BDNF levels increased. And it was also found that BDNF levels in the hippocampus increased in antidepressant-treated MDD patients' brain samples after death [17]. It suggested that decreased BDNF concentration was associated with anxiety and depression-like behavior, and preclinical studies also proved this and found something new. The relation between BDNF-TrkB signaling and anxiety and depression-like behavior in different brain regions was not consistent. (Table 1)

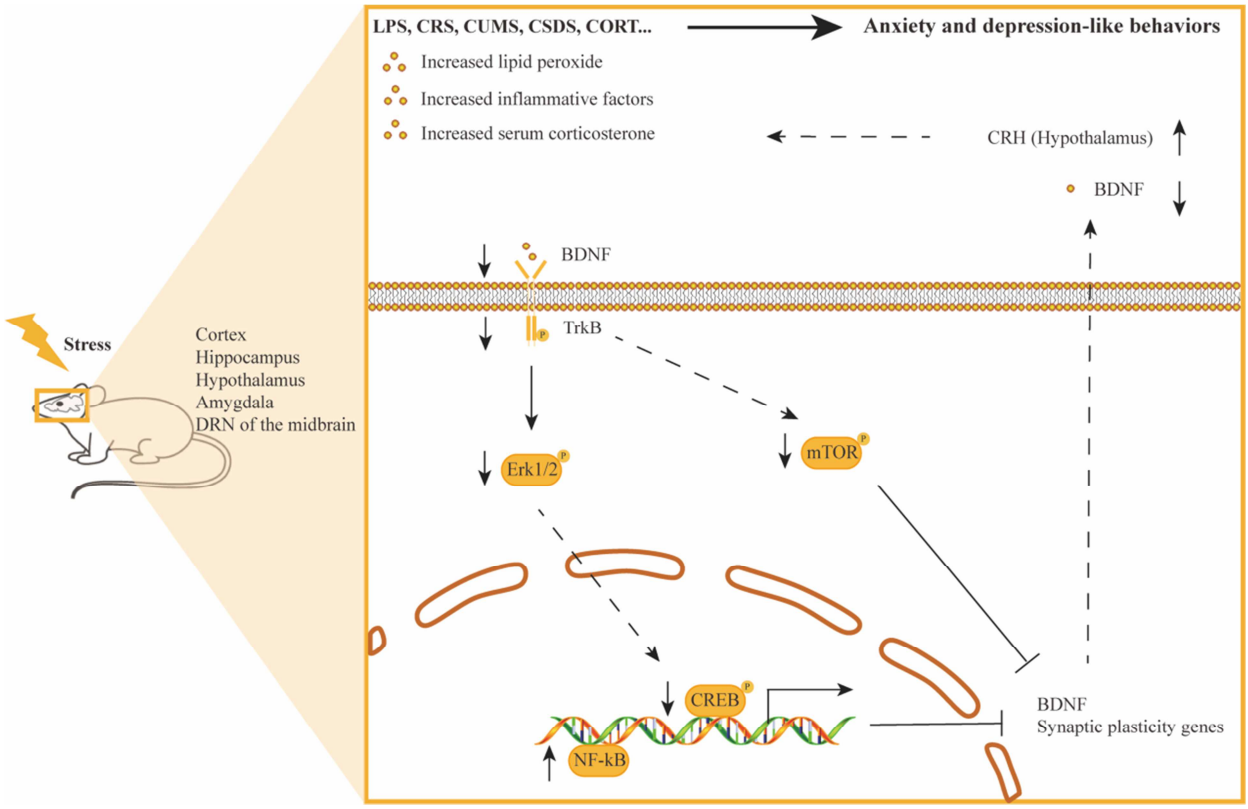

Figure 1. *Impaired BDNF-TrkB signaling pathway in anxiety and depression-like behaviors.*

Table 1. *The alteration of BDNF and TrkB in different brain regions in anxiety and depression-like behavior.*

Pathway	Animal	Paradigm	Phenotype		Brain regions	Before treatment		After treatment		
			Anxiety-like behaviors	Depression-like behaviors		BDNF	TrkB	BDNF	TrkB	
BDNF	Rats	LPS	-	-	CT, Hip	↓	-	-	-	[18]
BDNF	Mice	CUMS	Yes	Yes	CT, Hip	↓	-	-	-	[19]
BDNF-TrkB	Rats	CRS	-	Yes	CT, Hip	↓	↓	↑	↑	[20]
PIK3CA-AKT1-NRF 2/BDNF	Rats	OBX	Yes	Yes	CT, Hip	↓	↓	↑	↑	[21]
Nrf2/BDNF	Mice	CORT	Yes	Yes	CT, Hip	↓	-	↑	-	[22]
BDNF	Rats	LH	-	-	PFC, Hip	↓	-	-	-	[23]

Pathway	Animal	Paradigm	Phenotype		Brain regions	Before treatment		After treatment		
			Anxiety-like behaviors	Depression-like behaviors		BDNF	TrkB	BDNF	TrkB	
BDNF	Mice	LPS	Yes	Yes	PFC, Hip	-	-	↑	↑	[24]
BDNF-TrkB	Mice	LPS	-	Yes	PFC, Hip	↓	↓	-	↑	[25]
BDNF-TrkB	Rats	CUS	Yes	-	PFC, Hip	↓	↓	↑	↑	[26]
BDNF-TrkB	Rats	Immune system activation	Yes	Yes	PFC, Hip	↓	↓	-	-	[27]
BDNF-ERK-CREB	Mice	Methamphetamine withdraw	Yes	Yes	PFC, Hip	↓	-	-	-	[28]
BDNF/VEGF	Mice	Burn	Yes	Yes	PFC, Hip	↓	-	↑	-	[29]
BDNF-CREB	Rats	CUMS	Yes	Yes	PFC	↓	-	↑	-	[30]
BDNF-HCN1	Rats	SPS&S	Yes	Yes	PFC	↓	-	↑	-	[31]
mTOR-BDNF	Rats	CUMS	Yes	Yes	PFC	↓	-	↑	-	[32]
BDNF-TrkB-Akt	Mice	Subchronic arsenic exposure combined with reserpine	Yes	Yes	PFC	↓	↓	-	-	[33]
TrkB/Hsp70	Hamsters	CUMS	Yes	Yes	PFC, Hip, Amy, Ht	-	↓	-	↑	[34]
BDNF	Rats	LPS/IL-1β	-	-	Hip	↓	-	-	-	[35]
BDNF	Rats	CUMS	Yes	Yes	Hip	↓	-	-	-	[36]
BDNF	Rats	CUMS	-	Yes	Hip	↓	-	↑	-	[37]
BDNF	Rats	EM	Yes	Yes	Hip	↓	-	-	-	[38]
BDNF	Mice	HFD	No	Yes	Hip	↓	-	-	-	[39]
BDNF	Mice	FST	-	Yes	Hip	-	-	↑	-	[40]
BDNF	Mice	CD	Yes	Yes	Hip	↓	-	-	-	[41]
BDNF-TrkB	Mice	A$\beta_{1\text{-}42}$	Yes	Yes	Hip	↓	↓	↑	↑	[42]
BDNF-CREB	Rats	PM2.5	Yes	Yes	Hip	↓	-	-	-	[43]
BDNF-TrkB-CREB	Mice	CORT	No	Yes	Hip	↓	↓	↑	↑	[44]
BDNF-TrkB-CREB	Mice	Noise	Yes	Yes	Hip	↓	↓	↑	↑	[45]
BDNF-TrkB-CREB	Mice	CRS	Yes	Yes	Hip	↓	-	↑	↑	[46]
BDNF-TrkB-CREB	Rats	CUS	Yes	Yes	Hip	↓	-	↑	-	[47]
BDNF-TrkB-CREB	Rats	CUS	Yes	Yes	Hip	↓	↓	-	-	[48]
BDNF-TrkB-CREB-ERK	Mice	CUMS	Yes	Yes	Hip	↓	↓	↑	↑	[49]
PGC-1α-FNDC5-BDNF	Rats	CUMS	Yes	Yes	Hip	↓	-	↑	-	[50]
mTOR-BDNF	Mice	A$\beta_{1\text{-}40}$	Yes	Yes	Hip	↓	-	↑	-	[51]
AMPK/BDNF	Mice	IBD	-	Yes	Hip	↓	-	↑	-	[52]
BDNF-TrkB-Akt-Gsk 3b	Rats	CUMS	Yes	-	Ht	-	↓	-	↑	[53]
CREB-BDNF	Mice	LPS	Yes	Yes	ACC	↑	-	↓	-	[54]
NF-κB/BDNF	Mice	Hypoxia	Yes	Yes	Amy	↓	-	↑	-	[55]
BDNF-TrkB-CRH	Rats	Alcohol	Yes	-	Amy	↓	↓	↑	↑	[56]
BDNF	Rats	LH	-	-	NAc	↑	-	-	-	[23]
BDNF	Mice	CSDS	-	-	NAc	↑	-	↓	-	[57]
BDNF-TrkB	Mice	LPS	-	Yes	NAc	↑	↑	-	↓	[25]
BDNF	Rats	LH/Fst	-	Yes	DRN	-	-	↑	-	[58]
BDNF	Mice	CRS	Yes	Yes	LHb	↑	-	↓	-	[59]

Abbreviations: ACC, Anterior cingulate cortex; Amy, Amygdala; CD, Crohn's disease; CORT, Corticosterone; CRS, Chronic restraint stress; CSDS, Chronic social defeat stress; CT, Cortex; CUMS, Chronic unpredictable mild stress; CUS, Chronic unpredictable stress; DRN, Dorsal raphe nucleus; EM, Endometriosis model; FST, Forced swimming test; HFD, High-fat diet; Hip, Hippocampus; Ht: Hypothalamus; IBD, Inflammatory bowel disease; LH, Learned helplessness; LHb, Lateral habenula; LPS, Lipopolysaccharide; NAc, Nucleus accumbens; OBX, Olfactory bulbectomy; PFC, Prefrontal cortex; SPS&S, Single prolonged stress & electric foot shock.

2.1. Cortex

The cortex is the layer of gray matter on the surface of the brain. It occupies about 80% of the brain and is responsible for perception, thinking, language, memory, etc. BDNF can promote neuron growth and the formation of synapses in the brain. The inhibition of the BDNF-TrkB signaling in the cortex is correlated with anxiety and depression. Anxiety and depression-like behavior [19, 22, 24, 32] can be induced by CUMS, LPS, CORT, etc. The BDNF [18, 25, 30, 32] and TrkB [26, 34] levels were decreased in the cortex. With BDNF decreased, dendritic spine density was also decreased in the cortex, and rats were susceptible to depression-like behavior in the LH [23].

2.2. Hippocampus

The hippocampus is beneath the cerebral cortex, and in the medial temporal lobe of the brain. It occupies a little volume of the brain and is responsible for learning, memory, and emotion. The dentate gyrus (DG), CA1, CA2, and CA3 regions of the hippocampus were investigated in many studies. The inhibition of the BDNF-TrkB signaling in the hippocampus is associated with anxiety and depression. In addition to the above-mentioned CUMS, CORT, LPS-induced emotional disorder models, chronic restraint stress (CRS), olfactory bulbectomy (OBX), Aβ1-40, Aβ1-42-induced model, and DSS-induced IBD model, can also lead rodents exhibiting

anxiety and depression-like behaviors [21, 42, 46, 51, 52]. The expressions of BDNF and TrkB [19, 21, 44, 47] in the hippocampus were decreased. And to be specific, BDNF mRNA levels in the dorsal hippocampus were decreased in the CRS model [46]. BDNF levels and dendrite spine density in CA3 and DG regions of the hippocampus of the LH susceptible group were significantly decreased [23]. Inflammation can lead to anxiety and depression-like behaviors. LPS model or DSS-induced IBD model can cause systemic inflammation including brain inflammation. BDNF was decreased and the inflammatory factors elevated [18, 25] in the hippocampus, especially in CA2 [35], CA3 [25, 35], and DG [25, 35] in LPS-induced models. Decreased proliferating cells and activation of astrocytes and microglia could be seen in the IBD model [52]. The proliferating and survival cells decreased in the ventral, dorsal, and DG of the hippocampus [51], and autophagy cells increased [42] in the Aβ-induced models. CUMS cause decreasing BDNF and TrkB and has an influence on synaptic plasticity, which shows by the decreases of PSD95 level and synaptic spines in the hippocampal CA1 region, and the apoptosis of GFAP positive cells increased [47]. Early postpartum exposure to high doses of PM2.5 induced anxiety and depression-like behaviors in rats, impairing the synaptic number in the hippocampal CA1 region, and the synaptic plasticity in the hippocampal region with PSD95 and SYP decreased [43].

2.3. Hypothalamus

The hypothalamus is located under the dorsal thalamus and accounts for 0.3% weight of the brain. It involves the regulation of body temperature, feeding, endocrine, etc. The inhibition of the BDNF-TrkB signaling in the hypothalamus is associated with anxiety and depression. In CUMS paradigm, decreased TrkB mRNA in the VMH area of the hypothalamus was correlated with anxiety and depression-like behaviors [34]. Anxiety-like behavior can be seen in the acute sleep deprivation (SD) model, with decreased TrkB and p-Akt levels, elevated serum corticosterone and inflammation factor, and astrocyte activation in the hypothalamus [53].

2.4. Amygdala

The amygdala is located at the anterior end of the inferior horn of the lateral ventricle. It is mainly involved in memory, visceral and endocrine regulation, emotional activity, etc. The inhibition of the BDNF-TrkB signaling in the amygdala is associated with anxiety and depression. Decreased BDNF and p-TrkB in the amygdala were observed in the hypoxic stress and repeated alcohol exposure-induced models [55, 56]. In the hypoxic stress model, the brain exhibits oxidative stress and inflammation status, with increased MDA, decreased antioxidants like GSH, SOD, and CAT, and increased inflammatory factors [55]. And the serum corticosterone was elevated with the increase of CRH-positive cells in the PVN of the hypothalamus [56].

2.5. Anterior Cingulate Cortex (ACC)

ACC is located in the parahippocampal gyrus region and regulates emotional function. Activation of the ACC region and elevated BDNF levels are associated with anxiety and depression. In LPS-induced acute stress in rats, the ACC region was activated with an increasing level of c-Fos, and CREB, p-CREB, and BDNF levels were elevated in ACC [54]. Anxiety and depression-like behaviors can also occur in spared nerve injury (SNI) model. In this model, the ACC region was activated, and the expressions of BDNF and CREB were increased [54]. By knocking out CREB in ACC specifically, the expressions of CREB, p-CREB, and BDNF were all reduced, while the expressions of these proteins in the spinal cord were all increased, which could reduce anxiety and depression in rats [54]. With the silence of the ACC region, anxiety, and depression-like behaviors could be alleviated in rats [54]. The anti-BDNF antibody injection in bilateral ACC did not reverse the depression-like behavior of CUMS-induced mice [19]. This indicated that the expression of BDNF can be regulated by CREB.

2.6. Ventral Tegmental Area - Nucleus Accumbens (VTA-NAc)

VTA is located in the medial substantia nigra of the midbrain and the dorsal interpeduncular nucleus. NAc is located at the junction of basal ganglia and limbic system. VTA-NAc projecting has been proven in many studies [60, 61]. The activation of the BDNF-TrkB signaling in the VTA-NAc is associated with anxiety and depression. In the CSDS paradigm, the c-Fos protein was elevated in the VTA-NAc, and BDNF was increased in NAc [57]. Increased BDNF levels in the NAc can also be seen in LPS or LH-induced models [23, 25]. Meanwhile, the density of dendritic spines was also found higher than the control group, which indicated that regional differences in BDNF levels and dendritic spine density in the brain may be helpful to resist inevitable stress [23].

2.7. Dorsal Raphe Nucleus (DRN)

DRN is located in the midbrain and is the most important nucleus of serotonin neurons in the central nervous system. The inhibition of the BDNF-TrkB signaling in the DRN is associated with anxiety and depression. Infusion of BDNF in the midbrain near the DRN could reverse the depression-like behavior of rats [58]. Conditional knockout BDNF or TrkB in the DRN could not lead to anxiety or depression-like behavior, but conditional knockout TrkB could lead to loss of antidepressant efficacy, not BDNF [62]. Thus, we can see that TrkB in DRN may play an important role during antidepressants.

2.8. The Lateral Habenula (LHb)

The habenula is located above the posterior thalamus near the midline. It consists of the LHb and the medial habenula (MHb). The activation of the BDNF-TrkB signaling in the LHb is associated with anxiety and depression. In the CRS-induced model, the LHb was activated with an increased expression of c-Fos, and BDNF [59]. One study showed that

effort-based reward (EBR) contingency training could be a behavioral therapeutic intervention for depressive symptoms in rats, and the expression of BDNF in LHb decreased in EBR contingency training rats [63, 64]. After the BDNF was knockout in the LHb, CRS could not induce anxiety and depression-like behaviors in mice, and the expression of c-Fos and BDNF were not increased in the CRS paradigm [59].

3. The Function of BDNF in Antidepressant Treatment

In the combination of CUMS and 12-hour sleep deprivation (SD)-induced model, the depression-like behavior was alleviated with the hippocampal BDNF increased, but the anxiety-like behavior did not improve [49]. Conditional knockout BDNF in CA1 or DG of the hippocampus and DRN of the midbrain could not induce anxiety or depression-like behavior but could impair the antidepressant function [62, 65]. After the treatment of antidepressants, the BDNF cKO mice in CA1 or DG showed depression-like behavior compared with wild-type mice, but without anxiety-like behavior [65]. Conditional knockout TrkB in DRN also didn't show anxiety or depression-like behavior, and after the treatment of antidepressants, mice exhibited depression-like behavior but not anxiety-like behavior [62]. Injecting BDNF into DG, CA3 of the hippocampus, DRN of the midbrain, and VTA showed an antidepressant role but not an antianxiety function [58, 66, 67]. The injection of TrkB.T1 into NAc could lead to depression-like behavior, not anxiety [67]. Conditional knockout BDNF in LHb could prevent depression-like behavior but not anxiety-like behavior [59]. Thus, it seems like BDNF-TrkB signaling works weak in anxiety-like behaviors. (Table 2)

Table 2. *Preclinical studies of BDNF-TrkB signaling in anxiety and depression-like behavior.*

Pathway	Animal	Paradigm	Before treatment		After treatment		
			Anxiety-like behaviors	Depression-like behaviors	Anxiety-like behaviors	Depression-like behaviors	
BDNF-TrkB-CREB-ERK	Mice	SD 12h after CUMS	Yes	Yes	Not improved	Improved	[49]
BDNF	Mice	BDNF cKO in DG	No	No	Not improved	Improved in wildtype mice. Not improved in BDNF cKO mice	[65]
BDNF-TrkB	Mice	BDNF cKO in DRN	No	No	Not improved	Improved	[62]
BDNF-TrkB	Mice	TrkB cKO in DRN	No	No	Not improved	Improved in wildtype mice. Not improved in TrkB cKO mice	[62]
BDNF	Rats	BDNF infusion in DG	No	Yes	Not improved	Improved	[66]
BDNF	Rats	BDNF infusion in CA3	No	Yes	Not improved	Improved	[66]
BDNF	Rats	BDNF infusion in CA1	No	Yes	Not improved	Not improved	[66]
BDNF	Rats	BDNF infusion in DRN	No	Yes	Not improved	Improved	[58]
BDNF-TrkB	Rats	BDNF infusion in NAc	-	-	No	Yes	[67]
BDNF-TrkB	Rats	TrkB. FL infusion in NAc	-	-	No	No	[67]
BDNF-TrkB	Rats	TrkB. T1 infusion in NAc	-	-	No	Improved	[67]
BDNF	Mice	BDNF cKO in LHb	Yes	Yes	Not improved	Improved	[59]

Abbreviations: cKO, Conditional knockout; CUMS, Chronic unpredictable mild stress; DG, Dentate gyrus; DRN, Dorsal raphe nucleus; LHb, Lateral habenula; NAc, Nucleus accumbens; SD, Sleep deprivation.

Patients with endometriosis have a high incidence of anxiety and depression. By establishing the rat endometriosis model (EM), researchers found that MDA in the hippocampus of rats began to rise 14 days after EM, at which point depression-like behaviors began to appear. Until 21 days after EM, the rats' anxiety-like behaviors gradually increased, at which time corticosterone increased. The hippocampus had pro-oxidation status with increased TPO, decreased GSH and SOD activity, and low BDNF levels [38]. This indicates that in the EM model, decreased BDNF levels in the hippocampus lag behind anxiety and depression-like behaviors. And BDNF may be not the cause of anxiety and depression, it might be the mediator towards the progression or prevention of anxiety and depression.

This phenotype was also confirmed by the transgenic mice model. Most BDNF knockout mice died a few days after birth due to non-brain tissue effects such as cardiac dysplasia, but some individuals can survive for 2-4 weeks [68]. $BDNF^{+/-}$ mice didn't exhibit depression-like behavior [69]. No anxiety and depression-like behaviors were observed in BDNF conditional knockout mice in the forebrain, hippocampal CA1 and DG regions, and DRN of the midbrain, suggesting that the absence of BDNF in the hippocampus and the midbrain does not induce anxiety or depression-like behaviors [62, 65, 70, 71]. But the absence of BDNF in the forebrain and DG region of the hippocampus rather than the CA1 region plays a role in antidepressant treatment [65, 71], suggesting that genetic damage to BDNF-TrkB signaling pathways does not appear to lead to depression-like behavior, but will hinder the role of antidepressants [72]. Thus, BDNF may be a target for antidepressants, but not the only mediator of depression or anxiety.

3.1. Cortex

BDNF-TrkB is a target for antidepressant therapy. Duman's group first proposed that the common target of antidepressant

therapy may be BDNF and its receptor TrkB [20]. Researchers used electroconvulsive therapy, a variety of antidepressants, and a variety of non-antidepressant psychotropic therapies to treat the depression-like behavior of rats induced by CRS, to protect or reduce the damage of neurons by increasing the expression levels of BDNF and TrkB [20]. The following preclinical experiments also confirmed this. After treatment of anxiety and depression-like behavior induced by CUMS and LPS, the BDNF-TrkB signaling was activated, and the levels of BDNF and TrkB were increased [24-26], and anxiety and depression-like behaviors of rodents were improved. This suggests that the BDNF-TrkB pathway plays an important role in the pathophysiological processes of anxiety and depression-like behaviors. Antidepressant therapy was ineffective in $BDNF^{+/-}$ transgenic mice also proved it [69]. During antidepressant therapy, BDNF mediated the activation of TrkB and induced TrkB autophosphorylation, which led to the phosphorylation of CREB [69]. In LPS induced acute stress model, intraperitoneal (i. p.) injection of TrkB agonist 7, 8-dihydroxyflavonoids (7, 8-DHF) showed antidepressant effects, significantly alleviating the reduction of p-TrkB in the prefrontal cortex, while pre-injection of TrkB antagonist ANA-12 blocked the antidepressant effects of 7, 8-DHF [25]. Compared with wild-type mice, cortical TrkB-T1 subtype overexpressing mice showed decreased TrkB signaling in the brain [73] and decreased responsiveness to antidepressant drugs [69]. These studies suggest that the BDNF-TrkB signaling pathway plays a role in depression-like behavior and antidepressant effects.

3.2. Hippocampus

The BDNF-TrkB pathway in the hippocampus plays an important role in mediating the effect of antidepressant therapy. BDNF and TrkB mRNA levels increased in the granule cell layer of the DG region and conical cell layer of the CA3 and CA1 region after antidepressant or electroconvulsive therapy but remained unchanged after non-antidepressant psychotropic medication [20]. Multiple studies proved that BDNF and TrkB increased after the improvement of anxiety and depression-like behaviors after antidepressant therapy [21, 44, 46]. The combination of transcranial photobiomodulation (tPBM) and housing in an enriched environment (EE) can decrease the corticosterone concentration and activate the BDNF-TrkB-CREB signaling pathway in a noise stress-induced model [45]. Continuous or interval exercise preconditioning could mitigate the anxiety and depression-like behaviors of CUMS by activating the PGC-1α/FNDC5/BDNF pathway in the hippocampus [50]. Exercise can increase the number of hippocampal cell proliferation and survival in the Aβ-induced model [51]. Anti-inflammation treatment can activate the antioxidant factor Nrf2 signaling, to reduce inflammatory factors, and activate BDNF-TrkB signaling to improve anxiety and depression in LPS [24] and OBX-induced models [21]. In the CORT-induced model, fluoxetine treatment can activate the Nrf2 signaling pathway, and increase the BDNF expression to play an anti-anxiety depression effect [22]. But Nrf2 signaling was not the upstream signaling pathway of BDNF-TrkB signaling, for Nrf2 knockout mice can present elevated BDNF expression [22]. Liver hydrolysate can prevent depressive-like behavior in the DSS-induced IBD model by activating the AMPK-BDNF signaling to increase the proliferation of hippocampal cells and neurogenesis [52]. These results suggest that BDNF and its receptor TrkB may be the target of antidepressant therapy.

To verify the antianxiety and antidepressant functions of BDNF-TrkB, researchers infused BDNF into the DG, CA3, and CA1 areas of the bilateral hippocampus respectively in the LH paradigm, then they found that the DG and CA3 areas were activated with the improvement of depression-like behavior, which was confirmed by the increment of c-Fos and Elk-1 [66]. Ketamine can alleviate anxiety and depression-like behaviors, and Trk antagonist (K252a) can antagonize its therapeutic effect [47]. TrkB agonist 7, 8-dihydroxyflavone (7, 8-DHF) can exhibit antidepressant function by preventing the decrease of p-TrkB in DG and CA3 areas of the hippocampus in the LPS-induced model [25]. In the LH paradigm, inhibition of Trk (K252a) or MEK (U0126) blocked the antidepressant effect of BDNF, suggesting that the effect of BDNF is mediated by the activation of MEK and MAPK cascades [66].

3.3. Hypothalamus

After anti-inflammation treatment, with the PI3K-Akt and BDNF-TrkB signaling pathway in the hypothalamus activated, the neuroinflammation was alleviated, corticosterone concentration decreased, the activation of astrocytes in the hypothalamus was inhibited, and anxiety-like behavior was improved [53]. Infusing BDNF into the DG region of the hippocampus, TrkB mRNA in the VMH region of the hypothalamus was up-regulated, showing an antidepressant effect [34].

3.4. Amygdala

After the treatment of drugs or acupuncture, BDNF and p-TrkB were increased, and the anxiety and depression-like behaviors were alleviated [55, 56]. At the same time, the lipid peroxidation and inflammation levels in the brain and the serum corticosterone were decreased, with NF-κB signaling inhibited [55]. The expression of CRH in the PVN also decreased [56]. Injecting BDNF into the DG area, TrkB mRNA increased in the CeA of the amygdala, which performed an antidepressant function [34]. In the LPS paradigm, IL-33 was up-regulated in the amygdala, and IL-33 knockout mice exhibited an antianxiety effect with BDNF level increased in the amygdala [74]. Injecting TrkB antagonists, ANA-12, in the amygdala can prevent the increase of CRH in PVN, and alleviate the anxiety-like behavior of rats [56]. This indicated that activating BDNF-TrkB signaling could decrease the corticosterone level by regulating the CRH-positive neurons in PVN.

3.5. VTA-NAc

BDNF protein in NAc was thought to be derived from VTA [75]. Infusing BDNF in VTA for 1 week, the latency of immobility was shortened by 57%, which means that the rats

showed depression-like behavior [67]. Bilateral NAc infusion of TrkB antagonist, ANA-12, showed an antidepressant effect by preventing the elevated p-TrkB level [25]. To study the function of TrkB in NAc, rats received an intra-NAc full-length (TrkB. FL) or truncated (TrkB. T1) TrkB AAV injection. Compared with TrkB. FL and control groups, the injection of TrkB. T1 into NAc prolonged the latency of immobility by almost five times, showing an antidepressant-like effect [67].

3.6. LHb

The stimulation of LHb seems can increase the BDNF level in other tissues. A woman diagnosed with MDD treated with deep brain stimulation (DBS) of the LHb, was found an increased level of BDNF in the serum [76]. LHb lesions can improve the inflammatory response of the hippocampus and inhibit the activation of the hippocampal NF-κB pathway and the expression of inflammatory factors [77]. Inhibiting the function of LHb can increase the expression of BDNF and TrkB in the hippocampus [77, 78].

4. The Downstream and Upstream Molecular of BDNF-TrkB Signaling

The decrease of p-ERK was found in anxiety and depression models [79-81], and MKP-1, the negative regulators of ERK1/2 signaling, was increased [28]. Infusing MEK inhibitor U1026 into the medial prefrontal cortex (mPFC) or dorsal hippocampus (dHP), rats showed anxiety and depression-like behavior, and the expression of p-CREB decreased [82]. As the up-regulation of p-ERK and p-CREB, BDNF increased and the anxiety and depression-like behaviors were alleviated [49, 83].

The decrease of p-CREB was found in anxiety and depression models [84-86], along with hypomyelination and impaired synaptic plasticity [47, 48, 86], and the decreasing BDNF [30, 49]. With the increasing expression of p-CREB after treatment, the myelination was increased, which was confirmed by the increasing MBP, and the synaptic plasticity was improved [47, 86]. The expression of BDNF also increased [87, 88].

The decrease of p-mTOR was found in anxiety and depression models [51, 89, 90], along with decreased synaptic plasticity [90]. After antidepressant treatment, the expression of p-mTOR increased [91, 92], and the therapeutic effect could be inhibited by an mTOR inhibitor [92, 93], blocking the enhancement of excitatory synaptic transmission [32]. Depression-like behavior was observed in mice by unilaterally injecting siRNA into the mPFC to reduce the expression of mTOR. The expression of BDNF in the cortex decreased, and the dysregulation of the release of serotonin and glutamate in the DRN was observed [94].

Increased serum corticosterone, inflammation factors, and oxidative stress status were observed in anxiety and depression models [41, 95, 96], along with the activated astrocyte and microglia [96, 97]. In these models, the expression of TLR4 and NF-κB was increased [26, 41, 98]. As the increase of TLR4, TLR4-MyD88-NF-κB signaling was activated, and the inflammation factors were increased [95, 96]. Anti-inflammation treatment can inhibit the NF-κB signaling in the LPS-induced model, and alleviate anxiety and depression-like behaviors by decreasing the inflammation factors and the activated astrocyte and microglia and increasing the expression of BDNF [55, 99]. The increase of BDNF in NAc and LHb can lead to depression-like behavior [67, 77] but inhibition of the activated NF-κB signaling pathway to alleviate the inflammation in NAc and LHb can improve anxiety and depression-like behavior in male mice [77, 100].

5. Conclusions

In this review, we summarized the function of BDNF-TrkB signaling in different brain regions and its antidepressant effect. In all, the inhibition of the BDNF-TrkB signaling pathway in the cortex, hippocampus, hypothalamus, amygdala, and DRN, and the activation of the BDNF-TrkB signaling pathway in ACC, NAc, and LHb is associated with the development of anxiety and depression-like behavior. Studies have shown that the increased BDNF is related to high synaptic plasticity. This indicated that different brain regions have different regulatory effects on anxiety and depression-like behaviors, which requires further exploration. Due to limited studies of BDNF-TrkB signaling in the brain except for the cortex and hippocampus, the role of elevated BDNF-TrkB levels in ACC, NAc, and LHb leading to anxiety and depression-like behaviors remains to be elucidated. The impaired BDNF-TrkB signaling is a mediator, not the cause, of anxiety and depression-like behaviors. It can be regulated by the mTOR, NF-κB, PGC-1α-FNDC5, and AMPK signaling pathways. Decreased BDNF makes the body more susceptible to anxiety and depression. BDNF-TrkB signaling pathway plays a key role in antidepressant treatment. Without BDNF, anti-anxiety and anti-depression treatments will not work, and correspondingly, drugs or physical treatment targeting to improve the BDNF-TrkB level are inclined to alleviate the symptom of depression. Therefore, during the treatment of anxiety and depression, efforts can still be made to increase the level of BDNF. But it is still necessary to pay attention to changes in its upstream and downstream pathways in order to accurately treat and prevent the occurrence of anxiety and depression.

Abbreviations

AAV: Adeno-associated virus
ACC: Anterior cingulate cortex
Akt: Protein kinase B
AMPK: AMP-activated protein kinase
BDNF: Brain-derived neurotrophic factor
CAT: Catalase
CeA: Central amygdaloid nucleus
cKO: Conditional knockout

CORT: Corticosterone
CREB: cAMP response element binding protein
CRH: Corticotropin releasing hormone
CRS: Chronic restraint stress
CSDS: Chronic social defeat stress
CUMS: Chronic unpredictable mild stress
DBS: Deep brain stimulation
DG: Dentate gyrus
dHP: Dorsal hippocampus
DRN: Dorsal raphe nucleus
EBR: Effort-based reward
ECT: Electroconvulsive therapy
EE: Enriched environment
ERK: Extracellular regulated protein kinases
EM: Endometriosis model
FNDC5: Fibronectin type-III domain-containing protein 5
GFAP: Glial fibrillary acidic protein
GSH: glutathione
IBD: Inflammatory bowel disease
LH: Learned helplessness
LHb: Lateral habenula
LPS: Lipopolysaccharide
MAPK: Mitogen-activated protein kinases
MBP: Myelin basic protein
MDA: Malondialdehyde
MDD: Major depressive disorder
MEK: Mitogen-activated protein
MHb: Medial habenula
mPFC: Medial prefrontal cortex
mTOR: Mammalian target of rapamycin
NAc: Nucleus accumbens
NF-κB: Nuclear transcription factor-κB
Nrf2: NF-E2-related factor 2
OBX: Olfactory bulbectomy
PGC-1α: PPAR-γ coactivator 1 alpha
PI3K: Phosphatidylinositol-3 kinase
PSD95: Postsynaptic density protein 95
PVN: Paraventricular nucleus
$P75^{NTR}$: P75 neurotrophin receptor
SD: Sleep deprivation
SNI: Spared nerve injury
SOD: Superoxide dismutase
SYN: Synaptophysin
TLR4: Toll-like receptor 4
tPBM: Transcranial photobiomodulation
TPO: Thrombopoietin
VMH: Hypothalamic ventromedial nucleus
VTA: Ventral tegmental area
7, 8-DHF: 7, 8-dihydroxyflavone

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