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Chapter 2

Neurotrophic Factors and Major Depressive Disorder

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Additional information is available at the end of the chapter

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1. Introduction

Major depressive disorder (MDD) is a serious disorder that affects approximately 17% of the population at some point in life, resulting in major social and economic consequences [1]. There is still very little known about the neurobiological alterations that underlie the pathophysiology or treatment of MDD. There is increasing evidence suggesting that brain-derived neurotrophic factor (BDNF), neurotrophin-3, and fibroblast growth factor (FGF) systems are altered in different tissue samples, including post-mortem brain tissue, cerebrospinal fluid, and blood from patients with MDD. Neurotrophins are a family of secreted growth factors that regulate survival, growth, differentiation and maintenance of neurons in both the central nervous system and the peripheral nervous system [2] and their reduced availability can result in increased cellular vulnerability or even cell death. It has been postulated that the enhanced and prolonged secretion of neurotrophic factors in response to antidepressant treatment could promote neuronal survival and protect neurons from the damaging effects of stress. These studies have led to the formulation of the neurotrophic hypothesis of depression, which proposes that reduced neurotrophic factors levels predispose to depression, whereas increases neurotrophic factors produce an antidepressant action.

2. Brain-Derived Neurotrophic Factor (BDNF) in Major Depressive Disorder (MDD)

The *BDNF* gene is located on chromosome 11p13 and is synthesized as the precursor pre-pro-BDNF that is cleaved into pro-BDNF, which is then further cleaved into the 27-kDa mature protein [3]. BDNF plays an important role in the survival, differentiation, and outgrowth of various neurons in the peripheral and central nervous systems during development [2]. It is also involved in nerve regeneration and maintenance of structural integrity and neuronal

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plasticity in the adult brain, which includes the regulation of synaptic activity and neurotransmitter synthesis [4]. Thus, a pathological alteration of BDNF level can lead to defects in neuronal maintenance and neural regeneration as well as structural abnormalities and reduced plasticity that can impair an individual's ability to adapt to traumatic situations. Indeed, many pre-clinical and clinical studies implicate the modulation of BDNF expression in the behavioral manifestations of depression [5].

BDNF has shown antidepressant-like effects in animal models of depression. For instance, in the forced swim test and learned helplessness models of depression, BDNF infusion into the midbrain alleviated depressive behavior [6]. Moreover, a single bilateral infusion of BDNF into the dentate gyrus (DG) of the hippocampus had an antidepressant effect in both paradigms [7].

Various stressors can suppress *BDNF* mRNA and protein levels in different brain regions particularly in the hippocampus [8], which is associated with the development of depressive behavior. However, other reports found the contrary or else no changes in BDNF expression in animal models of depression and antidepressant efficacy [9-10]. Acute and chronic stress also increase hippocampal *BDNF* mRNA and protein levels [11-12], and it has been speculated that this could serve as a protective mechanism to offset the destructive effects of stress in the hippocampus.

Several classes of antidepressant increase BDNF level in the healthy rodent brain with chronic treatment, and also reverse stress-induced downregulation of BDNF [5]. Thus, regardless of their primary mechanism of action, antidepressants share the ability to rapidly activate signaling through the TrkB receptor and induce a long-lasting increase in BDNF production [13]. However, they fail to produce any behavioral changes in transgenic mice with reduced BDNF levels or TrkB signaling, whereas wild-type mice exhibit a normal behavioral response [14], demonstrating that BDNF release and TrkB signaling are not only sufficient but also necessary for antidepressant-like behavioral effects.

Electroconvulsive seizures increase mRNA levels of both *BDNF* and *TrkB* in the rat hippocampus, and chronic seizures blocked the downregulation of *BDNF* transcript level in the hippocampus in response to restraint-induced stress [15]. Repetitive transcranial magnetic stimulation (rTMS) is increasingly being used as a therapeutic tool to treat depressive disorder, based on reports that rTMS increases *BDNF* mRNA and protein in the rat hippocampus [16], similar to effects observed after administration of antidepressants or electroconvulsive seizures, which suggest that rTMS and antidepressants likely share a common molecular mechanism of action.

Several studies of post-mortem brain samples have implicated BDNF as a factor in the pathophysiology of depressive disorders; in one report, BDNF and TrkB levels were reduced in the hippocampus of patients with depressive disorder [17]. Given that BDNF expression is downregulated in response to stress, structural changes in the hippocampus of depressed individuals may be attributed in part to reductions in BDNF and TrkB levels [18]. In patients with depression, a decrease in prefrontal cortical volume is correlated with decreased BDNF and TrkB levels [19]. These findings indicate that depression affects BDNF expression in limbic regions. As observed in animal models, postmortem tissue samples from human subjects show

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increased BDNF levels in the hippocampus and cortex after long-term antidepressant use as compared to untreated subjects [20].

The Val66Met polymorphism is located in the pro-BDNF sequence, which is cleaved post-transcriptionally; while not affecting mature BDNF protein function, it has been shown to alter activity-dependent BDNF secretion in cultured cells [21], as well as intracellular distribution, packaging, and release of the BDNF protein in vitro [22]. Interestingly, mutant mice carrying the Val66Met polymorphism show reduced BDNF secretion but no differences in the level of total BDNF [21]. Moreover, hippocampal volume is reduced in mice with the BDNF Met/Met or Val/Met allele as compared to wild-type mice. Our research found that the presence of the Val66Met polymorphism was not significantly correlated with serum BDNF levels in depressive patients nor in control subjects. Postmortem analyses and imaging studies have found that depressive patients have significantly smaller hippocampal volumes compared to controls, which is reversed by antidepressant treatment [23]; smaller volumes were also observed in both patients and controls carrying the Met-BDNF allele as compared to individuals that were homozygous for the Val-BDNF allele. It was therefore concluded that Met-BDNF allele carriers may be susceptible to depression due to smaller hippocampal volumes [24]. Our laboratory has also demonstrated that the Val66Met allele frequency was similar among depressed and non-depressed subjects, consistent with previous studies in Asian populations [25-26]; however, an association between the BDNF Val66Met polymorphism and depression has been reported in a geriatric Chinese population [27]. A significant genetic association between the BDNF Val66Met polymorphism and treatment response in depressed patients was detected in a meta-analysis demonstrating that Val/Met heterozygous patients had a better response rate than Val/Val homozygous patients, especially among Asians [28]. Moreover, Met allele carriers showed a favorable response to antidepressant treatment [29]. However, other studies have not found any link between genetic variation in *BDNF* and antidepressant treatment response or remission [30-31]. The results from these studies indicate that the association between BDNF polymorphisms and the manifestation of depressive disorder symptoms or antidepressant efficacy remains controversial.

Suicide is a major public health problem linked to depression. *BDNF* and *TrkB* mRNA and BDNF protein levels were significantly reduced in both the prefrontal cortex and hippocampus of suicidal as compared to non-suicidal subjects [32]. BDNF downregulation was also observed in the hippocampus and prefrontal cortex of drug-free suicidal patients as compared to non-suicidal controls. In addition, suicidal subjects receiving antidepressant treatment showed no changes BDNF level, suggesting that psychotropic drugs counter the decrease in BDNF associated with depression [33]. DNA methylation at specific CpG sites in the *BDNF* promoter/exon IV was detected when postmortem brains samples from suicidal subjects were compared to those of non-suicidal controls. These findings support a role for the BDNF pathway in suicidal behavior associated with depression.

BDNF is present in human blood, although it is more highly concentrated in brain tissue. It was previously reported that BDNF could cross the blood-brain barrier, and that serum and brain BDNF levels showed similar changes during aging in rats, suggesting that the former is a reflection of the latter [34]. Serum BDNF level was markedly lower in depressed than in

healthy control subjects and was negatively correlated with depression severity, an effect that was more pronounced in females [35]. Similar findings were reported in another study, which also found greater changes in serum BDNF protein level in female but not in male patients treated with antidepressants during a 4-week period [36]. Some studies report that serum BDNF level is negatively correlated with depression severity [37-38]. Other investigators have found that plasma BDNF level is positively correlated with scores on the Hamilton Depression Rating Scale [39], although our own research did not substantiate these findings [40]. Serum BDNF level is determined by at least eight independent factors: time of blood withdrawal, time of storage, food intake before sampling, urbanicity, age, sex, smoking status, and drinking behavior [41]. However, the conflicting data from various studies suggest that other factors are likely to modulate BDNF level in depression.

3. Glial cell line-Derived Neurotrophic Factor (GDNF) in MDD

Glial pathology in depressive disorder is well-documented by a number of quantitative studies on postmortem fronto-limbic brain regions. The density of astrocyte cell bodies immunoreactive for glial fibrillary acidic protein (GFAP) is consistently reduced in brain tissue specimens from depressed individuals, as is the expression of astrocyte proteins such as GFAP, GDNF, connexins, glutamate transporters, and glutamine synthetase [42]. Astrocytes play essential roles in maintaining brain homeostasis and neuronal functions, and also mediate innate immunity and inflammatory responses in the brain. GDNF is a member of the transforming growth factor β superfamily that was isolated and purified from the conditioned medium of cultured rat glial cells of the B49 cell line [43]. GDNF consists of 134 amino acids with near-identical sequence in rats and humans. The widespread distribution of GDNF and its receptors in various regions of the adult brain suggests a role in maintaining neuronal circuits in the mature central nervous system (CNS) [44]. An increase in astrocyte GDNF synthesis and protein expression is believed to play an active role in neuronal survival and plasticity after excitotoxic damage [45], while experimental strategies of GDNF delivery by astrocytes have shown neuroprotective effects in vivo for dopaminergic neurons [46].

Animal studies have revealed that GDNF affects cognitive function, including learning and memory [47], while GDNF infusion increases hippocampal neurogenesis [48]. $GDNF^{+/-}$ mutant mice show abnormal hippocampal synaptic transmission [49], and GDNF overexpression in astrocytes of the hippocampal CA1 region can improve spatial learning and memory performance in cognitively impaired aging rats by enhancing local cholinergic, dopaminergic, and serotonergic transmission [50].

Several different classes of antidepressant including amitriptyline, clomipramine, mianserin, fluoxetine, and paroxetine have been shown to increase *GDNF* mRNA expression and protein secretion in rat C6 glioblastoma cells, while amitriptyline increased transcript expression in rat astrocytes when administered at concentrations comparable to those used in clinical trials. The results indicate that these drugs act through modulation of GDNF to improve the function of both glia and neurons [44].

Some animal studies have reported that chronic treatment with several classes of antidepressant or mood stabilizer has no affect on *GDNF* mRNA and protein expression in various areas of the rat brain [51-52]. However, in Flinders Resistant Line rats, chronic lithium treatment increased GDNF protein in the frontal and occipital cortices, decreased GDNF in the hippocampus, but did not alter GDNF level in the striatum [53]. In a rat model of chronic unpredictable stress-induced depression, *GDNF* mRNA and protein levels were significantly decreased in the hippocampus; this was reversed by clomipramine treatment [54]. The neuroprotective effects of clomipramine in the hippocampus suggest that GDNF is a viable target for novel antidepressant drugs. Chronic stress increased DNA methylation and histone modification in the promoter region of the *GDNF* gene and altered the control of behavioral responses in animal models of depression, effects that were reversed by antidepressant treatment [55].

The reduction in the volume of the cortex and limbic system that is observed in depressed patients is primarily associated with a decrease in glial cell numbers and to a lesser degree with decreased neuronal density and size [42]. In postmortem brain tissue from a small number of subjects with recurrent depression, increased GDNF level was detected in the parietal cortex relative to controls, and it was postulated that a loss of neurons and glia leads to an upregulation of GDNF as a compensatory response, which has also been reported in brain injury and animal models [56].

Electroacupuncture (EA) stimulation has been used for several decades to treat various mood disorders. A recent meta-analysis of 20 clinical trials found that acupuncture monotherapy was as effective as antidepressant treatment in terms of treatment response and alleviating the severity of symptoms [57]. Serum GDNF was increased by treatment with EA or fluoxetine in depressed patients and was associated with decreased Hamilton Depression Rating Scale scores in depressed patients [58]. In rats with transection of the medial forebrain bundle, EA upregulated *GDNF* mRNA expression in the brain [59]; acupuncture was also found to stimulate GDNF expression in the brain of adult cats [60]. These results suggest that EA can improve psychological symptoms of depression by altering *GDNF* expression, thereby halting or slowing neurodegeneration.

As in the case of antidepressants, the therapeutic effects of electroconvulsive therapy (ECT) involve stimulation of proliferation in neural progenitors via upregulation of specific signal transduction pathways [61]. ECT stimulates glial cell proliferation in the prefrontal cortex of rats by causing a reduction in the expression of *Sprouty2*, an inhibitor of cell proliferation [62]. ECT was also shown to decrease GDNF concentration in the hippocampus and striatum of the adult rat brain [63], although it is unknown whether this is due to decreased synthesis or increased release of the protein. However, it underscores the finding that acute and chronic ECT enhanced the mRNA expression of the GDNF receptor in the dentate gyrus of the hippocampus in rats [51]. Our research has demonstrated that serum GDNF level rises following ECT in patients with drug-resistant depression.

Adult mice heterozygous for a null mutation at the *GDNF* locus exhibited a lower level of *GDNF* mRNA in all brain regions examined. These mice also showed significant behavioral deficits in the Morris water maze spatial learning paradigm [47]. Overexpression of a *GDNF*

transgene in hippocampal astrocytes induced the recovery of spatial cognitive abilities in aged rats [50]. GDNF concentration was positively correlated with performance on the Wisconsin Card Sorting Test (WCST) conceptual level responses and negatively correlated with performance on the WCST preservative errors in depressed patients [64]. Moreover, increased plasma GDNF level was positively correlated with the Digit Span Test backward score and negatively associated with Trail Making Test B performance in late-onset depression patients [65]. These results indicate that increased GDNF may protect against neuronal damage and consequent cognitive impairment in depressed individuals.

A recent study evaluated the effect of 21 single nucleotide polymorphisms in the *GDNF* gene on the efficacy of paroxetine in patients with MDD, and found that the A allele for rs 2973049 and the T allele for rs 2216711 were correlated with paroxetine response and gender [66].

The neuroprotective effects of GDNF may be due in part to its ability to protect neurons from oxidative stress. Postmortem studies indicate that patients with recurrent depressive disorder have increased oxidative stress in some brain regions, such as the frontal cortex, thalamus, and putamen [67]. Subchronic infusion of recombinant human GDNF increased superoxide dismutase, catalase, and glutathione peroxidase activities in rat striatum, suggesting that GDNF may have antioxidant properties [68]. GDNF also protected human mesencephalic neuron-derived cells from oxidative injury [69].

We found that serum GDNF level was decreased in antidepressant-free patients with MDD and was not correlated with depression severity. We also found that decreased serum GDNF level in naive patients recovered to normal levels after treatment with antidepressants [70]. Reduced *GDNF* mRNA expression was detected in peripheral white blood cells of MDD patients in a depressive state but not in those in a remissive state, suggesting that the alteration in GDNF level is state-dependent [71]. Circulating serum GDNF level was also decreased in patients with late-in-life depression, and this was negatively correlated to the disease severity [72]. However, plasma GDNF level was higher in euthymic patients with bipolar disorder and in patients with late-onset depression [65,73]. This inconsistency may be due to confounding effects of age, gender, or concurrent physical illness. One study has shown that patients with bipolar and unipolar affective disorder in remission had a decreased GDNF level compared to unaffected controls, which was not correlated with antidepressant treatment [74].

4. Insulin-like Growth Factor (IGF) in MDD

There is increasing evidence that IGF-1 plays an important role in diseases affecting the CNS. IGF-1 increases the synthesis and activity of BDNF [75], and both are required for neuronal survival and synaptic plasticity in the brain [76]. IGF-1 also enhances proliferation, survival, differentiation, and maturation of all CNS cells and has demonstrated neurotrophic, neurogenic, and neuroprotective functions [77]. IGF-1 is the only neurotrophic factor known to be regulated by the immune system, the dysregulation of which is implicated in the pathogenesis of depression.

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The *Igf1* gene in humans is located on chromosome 12q22–23. IGF-1 is a small (7.5-kDa) polypeptide that, along with IGF-2, insulin, their respective receptors, and six IGF-binding proteins, constitute the insulin-like growth factor family [78]. IGF-1 and its receptor are widely distributed in all cell types of the adult brain. Although it can penetrate the blood-brain barrier, IGF-1 is also produced by various cells in the CNS and peripheral nervous system [79]. *Igf1* mRNA expression in the CNS is low during early organogenesis, but increases at later developmental stages [79]; after the brain is formed, low levels of expression are restricted to a few regions. However, the adult brain also receives IGF-1 from the serum where the peptide is abundant. Additionally, IGF-1 expression remains high in the adult brain, especially in areas with large projection neurons such as the cerebellum, olfactory bulb, hypothalamus, hippocampus, cortex, and retina [80].

Individuals with depression have reduced hippocampal volume as compared to controls. Post mortem and brain imaging studies have revealed atrophy in the hippocampus of depressed patients, which may be reversed by antidepressant treatment [23]. Peripheral infusion of IGF-1 induced neurogenesis in adult rat hippocampus, and IGF-1 stimulates proliferation in adult rat hippocampal progenitor cells [81], while in vitro studies found that IGF-1 increased the total number of progenitor cells and promoted the specification of a neuronal lineage from precursors [79]. Transgenic mice lacking IGF-1 or IGF-1R show severe delays in brain development [82]; mice overexpressing IGF-1 in the brain exhibit an increased numbers of neurons and synapses in the dentate gyrus, while IGF-1 knockout mice have a decreased number of granule cells in this region [83-84].

In animal models of depression, the specificity of the models used, the immune status of the tested animals, or animals' age and gender can influence the levels of growth factors including that of IGF-1. In one study using the Cre-loxP system to knock out the *Igf1* gene in the liver, hippocampal CA1 neurons, or both, IGF-1 deficiency at adulthood was sufficient to induce a depressive phenotype in mice, suggesting that low brain IGF-1 level heightens the risk for depression; moreover, these effects are not ameliorated by increased local IGF-1 production or transport [85]. A prenatal stress model of depression found no changes in peripheral IGF-1 levels between stressed and control rats, but a significant decrease was observed in the hippocampus and frontal cortex [79].

Early adverse experiences contribute to the development of vulnerability to stress and increase the risk of stress-related psychiatric disorders in adulthood. For instance, maternal separation during critical periods of brain development can lead to learning disabilities, behavioral anomalies, or psychiatric disorders in later life [86]. Repeated maternal separation of neonatal rats caused prolonged and abnormal fluctuations in the expression of BDNF and IGF-1 and their respective receptors TrkB and IGF-1R in the cerebral cortex [86]. Another study found that maternal separation alone or in combination with a single episode of restraint stress decreased the mRNA expression of *IGF-1R* and *IGF binding protein-2* in the adult rat hippocampus. Given that the activation of IGF signaling plays a role in development and neuroprotection of the CNS, this downregulation of IGF signaling likely contributes to the development of stress vulnerability in adulthood, which can in turn precipitate the onset of depression [87].

The potential antidepressant activity of IGF-1 has been examined in various animal models of depression in which behavioral tests such as forced swimming and tail suspension were used to evaluate antidepressant effects. These studies have consistently shown that IGF-1 treatment has antidepressant-like effects and normalizes behavioral disturbances in depressive animals [88-90]. In addition, repeated administration of fluoxetine induced the upregulation of IGF-1 and its receptor in the frontal cortex but a downregulation in the hippocampus [91]. IGF-1 level was also upregulated in the adult rat hippocampus after chronic administration of venlafaxine [92]

Increased IGF-1 level in the blood of depressed patients has been observed in clinical studies [93-94], while others have reported decreased peripheral IGF-1 concentration in patients, possibly due to overactivation of the hypothalamic-pituitary-adrenal axis. A recent study demonstrated that a low IGF-1 level in females and a high level in males can predict the incidence of depressive disorder 5 years later [95]. IGF-1 concentration was also found to decline during antidepressant treatment in patients, albeit only in responders [93].

5. Vascular Growth Factor (VGF) in MDD

VGF, originally cloned as a target of NGF regulation in PC12 cells, is also induced by BDNF in cortical and hippocampal neurons in vitro and in vivo [96]. The *VGF* gene has been highly conserved throughout evolution and is located on chromosome 7q22 in humans and chromosome 5 in mice. VGF contains a cyclic AMP response element-binding protein (CREB)-binding site within its promoter that is critical for BDNF-induced *VGF* expression; thus, CREB is a factor regulating both *BDNF* and *VGF* expression [97]. VGF also contributes to synaptic plasticity by inducing the secretion of BDNF or other neuromodulatory peptides in a positive feedback loop, and mediates the long-term effects of BDNF-induced synaptic strengthening through its activity at excitatory synapses [96]. VGF is also involved in regulating energy balance via hypothalamic and autonomic outflow pathways that govern peripheral energy expenditure [98]. VGF is widely expressed in neurons and is detected in the olfactory system and several areas of the brain, including the cerebral cortex, hypothalamus, and hippocampus [99].

$VGF^{+/-}$ mice have no gross abnormalities in brain morphology and exhibit normal anxiety levels. However, these mice show neurological and behavioral deficits akin to depression [100-102], suggesting that a reduced VGF level may account for depression in humans. Chronic treatment with different classes of antidepressant such as imipramine, fluoxetine, and duloxetine has been shown to modulate VGF expression [100-101,103], while infusion of VGF into the midbrain or hippocampus produces antidepressant effects in the learned helplessness paradigm of depression, as well as in the tail suspension and forced swim tests, which are used to evaluate the action of antidepressants [101-102]. In one of these studies, exercise increased VGF in the hippocampus of wild-type mice and induced an antidepressant-like response in the forced swim test; the increase was less pronounced in $VGF^{+/-}$ mice, which also failed to show behavioral improvement resulting from exercise in the forced swim test. Moreover, the administration of VGF peptide induced a robust, dose-dependent antidepressant-like re-

sponse in the forced swim and tail suspension tests. In another study, VGF-derived peptide protected primary cultures of rat cerebellar granule cells from serum and potassium deprivation-induced cell death in a dose-and time-dependent manner [104].

Chronic antidepressant treatment in adult rodents increases neurogenesis in the dentate gyrus of the hippocampus, which may be a common mechanism by which antidepressants induce their therapeutic effects [105]. VGF peptide similarly enhanced neurogenesis of hippocampal cells and may favor the differentiation of proliferating progenitors into neurons over glia [101]. Although the precise relationship between depression and neurogenesis remains to be elucidated, stimulating cell proliferation may be one way in which VGF exerts antidepressant effects.

ECT is a highly effective and rapid treatment for depressed patients who do not respond to antidepressants. While the molecular mechanisms underlying the therapeutic efficacy of ECT are not fully understood, it is thought that ECT and antidepressants increase the expression of select neurotrophic factors that reverse or block the atrophy and cell loss resulting from stress and depression. ECT was shown to increase the level of VGF in the hippocampus of rats [103,106], and a decrease in *VGF* mRNA level was observed in drug-free depressed patients with respect to controls, although there was no correlation between *VGF* mRNA levels and the severity of the illness. Interestingly, 12 weeks of treatment with escitalopram increased VGF expression albeit only in responder patients, suggesting that changes in the expression of the neuropeptide may explain the mechanism of the drug response [107].

In the European Genome-based Therapeutic Drugs for Depression study, nine psychiatric centers in eight European countries recruited 811 adult outpatients suffering from unipolar depression of at least moderate severity. These patients showed significant upregulation in leukocyte *VGF* mRNA expression level after 8 weeks of treatment in both responder and non-responder patients [108].

Findings from human postmortem studies of bipolar patients indicate that VGF is downregulated in the CA regions of the hippocampus and Brodmann's area 9 of the dorsolateral prefrontal cortex [109]. Importantly, VGF showed effects similar to those of lithium, which is used to treat bipolar disorder. However, another study found an increase in VGF23–62 peptide level in the cerebrospinal fluid of 16 patients diagnosed with MDD [110]. The association between *VGF* gene polymorphisms and depression or bipolar disorder has not been examined thus far.

6. Fibroblast Growth Factor (FGF) in MDD

FGFs and their receptors constitute an elaborate signaling system that is organized in dynamic spatial and temporal expression patterns. There are at least 23 members of the FGF family, 22 of which are distributed throughout the CNS in humans along with five FGF receptors. FGF1 and FGF2, which lack a signal sequence, are secreted and directly regulate intracellular signaling cascades in target cells. FGF ligands share a conserved central domain of about 120

amino acids that binds heparin and is required for stable FGF ligand-receptor interactions [111]. FGFRs are tyrosine kinase receptors with three immunoglobulin-like domains (D1, D2, and D3) [112].

FGF signaling has been implicated in a variety of mood disorders, including MDD. The neurotrophic hypothesis of depression posits that neurogenesis and neuronal plasticity are affected by the imbalance in growth factor levels. FGF2 attenuates the reduction in hippocampal volume and promotes hippocampal neurogenesis after traumatic brain injury in mice [113]. Post-mortem examinations have shown that the expression of FGF1, FGF2, and receptors FGFR2 and FGFR3 is decreased in the frontal cortical area in MDD relative to controls. FGF signaling is also upregulated by treatment with antidepressants [114]. A lower serum FGF-2 level has been reported in MDD patients, which may be reversed by antidepressants [115]. In an animal model, a single subcutaneous injection of FGF2 administered to rats on postnatal day 1 increased cell survival in the DG 3 weeks later, producing a larger hippocampus with more cells [116]; a similar effect was observed in the adult brain [112].

FGFR1 conditional knockout mice lacking *FGFR1* expression in the telencephalon at mid-neurogenesis showed that the *FGFR1* gene is required during hippocampal development [111] for the proliferation of hippocampal progenitor and stem cells [117]. Loss of FGFR1 function results in decreased proliferation of neural progenitor cells in the hippocampus and depletion of the FGF2-sensitive hippocampal neural stem cell pool, which leads to permanent atrophy of this brain area. $FGF2^{-/-}$ mice showed reduced numbers of cortical neurons by the end of neurogenesis, especially of large neurons in deeper cortical layers of the frontal cerebral cortex [118]. Progenitors of hippocampal granule cells in the DG in $FGF2^{-/-}$ mice showed reduced proliferation in response to kainic acid injection or middle cerebral artery occlusion, which was reversed by FGF2 injection [119]. Thus, FGF2 induces neurogenesis, alters neuronal morphology, and modulates gene expression in the hippocampus.

FGF2 has antidepressant-like effects when administered later in adulthood. FGF2 infusions had both antidepressant and anxiolytic effects in behavioral models of depression and anxiety [120]. FGF activity has also been linked to the response to antidepressant medications in humans, and some studies have found a correlation between *FGF* transcript expression and major depression.

Affymetrix microarray analyses of cortical brain regions detected a significant number of *FGF*-related ligand and receptor genes that are differentially expressed in depressed individuals, including *FGF1*, *FGF2*, *FGFR2*, and *FGFR3*, which are downregulated, and *FGF9* and *FGF12*, which are upregulated [114]. Depressed subjects receiving selective serotonin reuptake inhibitor (SSRI) treatment showed increased FGFR expression as compared to those who were not using these drugs. One recent study also demonstrated alterations in *FGF9* and *FGFR3* transcript expression in the locus coeruleus (LC) of individuals with MDD [121]. Serum FGF2 level in MDD patients was significantly lower than that of healthy controls [115], and in postmortem samples of MDD patients, single nucleotide polymorphisms in *FGF2* (rs1048201, rs1449683, and rs308393) were correlated with side effects and differential treatment response to antidepressants [122].

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7. Neurotropin-3 (NT3) in MDD

NT3 is a member of the neurotrophin family of proteins that supports the survival of specific types of neuron [123]. NT3 is distributed throughout the DG and promotes hippocampal plasticity by regulating neurogenesis via binding of TrkB and TrkC tyrosine kinase neurotrophin receptors [124].

NT3 has been implicated in the pathogenesis of depression and the therapeutic mechanism of antidepressants. Hippocampal atrophy has been consistently demonstrated as one of the predominant pathophysiological changes in subjects with a history of MDD, and is correlated with duration of the illness [125]. NT3 prevented the degeneration of noradrenergic neurons in the LC [126] that are associated with the pathophysiology of major depression [127]. NT3 infusions cause an upregulation in the mRNA level of *BDNF* in the cerebral cortex [128] and produces BDNF-like effects including the phosphorylation of cortical tyrosine kinase B [123]. NT3 may be involved in the modulation of BDNF signaling in differentiating hippocampal neurons [129], and was shown to modulate monoamine neurotransmitters such as 5-hydroxytryptophan and noradrenaline [130] and activate noradrenergic neurons in the LC [131]. Chronic stress causes structural changes and neuronal damage in the brain, especially in the hippocampus, which can lead to the development of depression [132]. *NT3* mRNA levels were upregulated in the DG and hippocampus in response to repeated immobilization stress in rodents [133]. NT3 is expressed throughout the hippocampus and promotes plasticity by regulating neurogenesis. A 500-ng dose of NT3 injected into the cerebral ventricle of mice at the onset of the dark period enhanced the time spent in non-rapid eye movement sleep [134]. Lithium and valproate, which are mood-stabilizing agents, increased hippocampal NT3 levels in an animal model of mania [135], highlighting a role for NT3 in mood disorders besides depression.

NT3 antagonizes the proliferative effects of basic FGF, and enhances neuronal differentiation, while blocking NT3 function leads to a decrease in neurogenesis [136]. In NT-3 mutant mice with brain-specific *NT3* deletion, the differentiation of the neuronal precursor cells was impaired in the DG, resulting in a decrease in the production of differentiated neurons [124].

Postmortem analyses have demonstrated altered levels of neurotrophic factor expression in the brains of patients with mood disorder. Serum NT3 levels were increased during acute mood states of bipolar depression patients as compared to euthymic patients and normal controls [137]. In another study, serum NT3 level in drug-free and medicated patients with bipolar disorder during manic and depressive episodes was increased relative to controls, while there was no difference between medicated and drug-free patients [138]. *NT3* mRNA was downregulated in peripheral white blood cells of patients with MDD and bipolar disorder during depressed and euthymic states, but not those in remission, suggesting that reduced *NT3* expression is state-dependent and associated with the pathophysiology of major depression [71]. However, in elderly MDD patients, NT3 levels in the cerebrospinal fluid were significantly elevated as compared to patients with Alzheimer's disease or mentally healthy controls [139]. The reason for these contradictory findings is unknown, but could indicate that there are other age-dependent factors that modulate the effects of NT3.

8. Nerve Growth Factor (NGF) in MDD

NGF was the first identified neurotrophin in a family of structurally similar growth factors. In the CNS, NGF is involved in neuronal survival, protection of sympathetic and cholinergic neurons against neurodegeneration, and in the modulation of the immune response as well as learning and memory [140].

NGF has demonstrated neuroprotective effects on basal forebrain cholinergic neurons in Alzheimer's disease patients [141]. However, the injection of NGF antibody was shown to induce the death of sympathetic neurons in mouse, rat, cat, and rabbit models [142]. Mouse models of anxiety, chronic stress, and depression involving learned helplessness, threatening or painful stimuli, maternal deprivation, and other factors induce a reduction in NGF in the frontal cortex, amygdala, hippocampus, and nucleus accumbens [143-145]. In MDD patients, serum NGF level is higher than in controls, and has been associated with the severity of depressive symptoms in women [146].

Whether alterations in NGF are state-or trait-dependent is under debate. In mood disorders, a state-related phenomenon appears and then disappears with mood state; in contrast, a trait-related phenomenon occurs regardless of variations in the clinical state. One study of in-and outpatients with mood disorders including uni-and bipolar depression and bipolar mania found no differences or changes in NGF levels in patients with depressive episodes and after 8 weeks of medical treatment [147], consistent with previous findings that NGF levels do not vary among depressed patients [148-150].

Nonetheless, several clinical studies have reported that serum NGF concentration is decreased relative to healthy controls in MDD patients [151-152], including those receiving duloxetine [153] and those experiencing depression late in life [154]. In contrast, other studies have reported increased NGF in patients with elevated levels of stress and severe depression [155]. The severity of washing symptoms is correlated with an upregulation in NGF in patients with obsessive-compulsive disorder [156], while another study found a positive correlation between plasma NGF level and disease duration in patients with bipolar mood disorders [157].

Various studies have investigated the effects of ECT on NGF levels in animals and humans. Electroconvulsive stimuli administered once daily for 8 days increased NGF level in the frontal cortex of adult rats [63]. Repeated exposure to electroconvulsive stimuli also increased TrkA and NGF protein levels in the rat hippocampus [158], suggesting that NGF may play a role in the mechanism of action of electroconvulsive treatment. In contrast to animal studies, ECT treatment has not been found to affect NGF levels in human patients. In patients with treatment-resistant major depression [159] or bipolar disorder with depression [160], NGF levels were not significantly increased by ECT, even with concurrent administration of antidepressants and psychotherapy.

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9. Conclusion

Several preclinical and clinical observations indicate that depression may be associated with the inability of neural systems to exhibit adaptive plasticity. Given the role of neurotrophic factors in neural and structural plasticity, and that depression and antidepressants exert opposite actions on neurotrophic factors expression and functions, it is apparent that neurotrophic factors signaling may be crucial in the pathophysiology of depression and in the mechanism of action of antidepressants. However, future work will be necessary to determine whether neurotrophic factors is a risk factor for initiation or maintenance or in the recovery process with respect to MDD and how its circuit-level function contributes at MDD stages. In addition, the search for more effective and applicable neurotrophic factors-based therapies is crucial.

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