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Involvement of Brain-Derived Neurotrophic Factor in Late-Life Depression

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Abstract

Brain-derived neurotrophic factor (BDNF), one of the major neurotrophic factors, plays an important role in the maintenance and survival of neurons, synaptic integrity, and synaptic plasticity. Evidence suggests that BDNF is involved in major depression, such that the level of BDNF is decreased in depressed patients and that antidepressants reverse this decrease. Stress, a major factor in depression, also modulates BDNF expression. These studies have led to the proposal of the neurotrophin hypothesis of depression. Late-life depression is associated with disturbances in structural and neural plasticity as well as impairments in cognitive behavior. Stress and aging also play a crucial role in late-life depression. Many recent studies have suggested that not only expression of BDNF is decreased in the serum/plasma of patients with late-life depression, but structural abnormalities in the brain of these patients may be associated with a polymorphism in the BDNF gene, and that there is a relationship between a BDNF polymorphism and antidepressant remission rates. This review provides a critical review of the involvement of BDNF in major depression, in general, and in late-life depression, in particular.

Keywords

BDNF; major depression; antidepressants; late-life depression; genetics

Major depressive disorder (MDD) is a major public health concern. It affects approximately 15% of the population at some point in their lives and is the leading cause of disability worldwide.[1] About 9 million people are diagnosed as having MDD each year in the United States alone, and the lost productivity and treatment expenses burden the U.S. economy by more than $43 billion per year.[2] Among elderly individuals (aged 65 years and older), 1% to 4% of the population exhibit MDD.[3] In hospitalized elderly persons, the occurrence of MDD ranges between 10% and 35%.[4,5] Major depressive disorder in elderly persons is associated with an increased number of suicide attempts and increased lethality.[6] In fact, suicide in the elderly population is twice as common as in the general population;[7] interestingly, MDD is one of the major causes of suicide in subjects with late-life depression because approximately 80% of people who commit suicide show depressive symptoms.[8] Alexopoulos et al.[9] studied the clinical characteristics that can identify elderly patients with depression at risk for suicidal ideation and found that contemporaneous severity of depression was the most important determinant of suicidal ideation over time.

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Late-life depression is a heterogeneous disorder, and multiple factors play important roles in this disorder. These factors include aging, medical conditions, and cerebrovascular diseases (reviewed in Smith et al.[10]). Major depressive disorder is often associated with cognitive deficits; this deficit is higher in late-life than in the younger population, however.[11] Butters et al.[12] showed that, relative to control subjects, patients with late-life depression perform poorer in all cognitive domains and more than half of these patients exhibit significant cognitive impairment. These cognitive impairments are associated with memory impairment, poor attention, and executive dysfunctions;[13,14] they often precede the onset of dementia and Alzheimer disease.[15,16] Because of several factors associated with late-life depression, the neurobiological mechanisms associated with this disorder are not clearly understood. Also, not all risk factors in late-life depression are late life in origin. Several factors that are critical in the onset of MDD in younger life may also be as important in late-life depression. One example is stress and stress-related hormones, which are important in early-life, and to some extent, in late-life depression. Also, MDD in early life may predispose a person to late-life depression. Thus, there is some commonality in the pathophysiological characteristics of early- and late-life depression.[17] As discussed subsequently, brain-derived neurotrophic factor (BDNF) is a critical neurotrophic factor that plays a crucial role in neural plasticity and cognition and is involved in depression. More recently, neurochemical and genetic studies indicate that BDNF may be a pathophysiological significance in late-life depression. This review focuses on the role of BDNF in depression during early and late life.

Structural Abnormalities in the Brain: Early- Versus Late-Life Depression

An emerging hypothesis suggests that the pathogenesis of MDD involves altered neural plasticity,[18] resulting in the inability of the brain to make appropriate adaptive responses to environmental stimuli.[19] The affective fronto-limbic circuitry, including the prefrontal cortices, the cingulate cortex, and several limbic structures (including the hippocampus), are highly involved in mediating these adaptive responses. Several lines of evidence demonstrate that these regions show structural and functional alterations in MDD. These include a reduction in cell number, density, cell body size, neuronal and glial density in frontal cortical or hippocampal brain areas, and parahippocampal cortex and cortical/laminar thickness.[20–24] In addition, studies in MDD subjects show changes in synaptic circuitry in anterior limbic cortex,[25] abnormal dorsolateral prefrontal cortical activity,[26] impaired synaptic connectivity between the frontal lobe and other brain regions,[27] neuronal atrophy, a decreased volume of the hippocampus,[28–30] a decreased number of neurons and glia in cortical areas,[31] and spatial cognition deficits.[32] In addition, changes in the number and shape of dendritic spines,[33,34] changes in the primary location of synapse formation, altered dendritic morphological characteristics of neurons in the hippocampus, and a decrease in length and number of apical dendrites[35] have been reported during stress in mice and rats. Furthermore, stress hinders performance on hippocampal-dependent memory tasks and impairs induction of hippocampal long-term potentiation (LTP). These studies clearly demonstrate impaired structural and functional plasticity in MDD.

Structural abnormalities have also been reported in the brain of subjects with late-life depression. For example, structural neuroimaging findings have shown decreased volumes of subcortical and limbic structures, such as subgenual anterior cingulate, caudate, putamen, hippocampus, and amygdala.[36–39] Individuals with late-life depression also show reduced activity in the prefrontal dorsolateral cortex and reduced functional connectivity between dorsolateral prefrontal cortex and anterior cingulate cortex.[10,40,41,42] It has been suggested that MDD-associated alterations in neuronal and glial cell population in the frontal and subcortical circuitry changes may be related to early- and late-life depression because glial reductions are more consistent in younger depressed subjects, whereas neuronal changes are

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more common in elderly depressed subjects.[32,43] White matter abnormalities also occur in patients with late-life depression, particularly in subcortical structures and their frontal projections, which are primarily associated with executive dysfunction (reviewed in Smith et al.[10] and Alex-opoulos[36]). Sheline et al.[44] showed greater hyper-intensities in several white matter tracts in subcortical regions in subjects with late-life depression, and volumes of some of these brain regions correlate well with executive functions. For example, whole brain white matter correlates with episodic memory, processing speed, and executive function; and whole brain gray matter correlates with processing speed.

Given the role of hippocampus in stress, memory, and cognition, several studies have examined this brain region in both early- and late-life depression. For those with MDD, it has been shown that hippocampal volume is smaller than in healthy subjects.[45] Similarly, a reduction in hippocampal volume in late-life depression has also been reported by many investigators[46–49] and has been further supported by meta-analyses performed in two separate studies.[45,50] In a positive emission tomography study, de Asis et al.[51] demonstrated deficits in bilateral activation of hippocampus of the geriatric depressed patients. These patients had memory deficits that correlated with lower hippocampal activity during both rest and activation. Ballmaier et al.[52] reported that hippocampal volumes differed between depressed patients and comparison subjects but not between patients with early- and late-onset depression. When statistical mapping was performed, they found that regional surface contractions were significantly pronounced in late-onsest compared with early-onset depression in the lateral posterior of the hippocampal CA1 subfield in the left hemisphere. Hippocampal surface contractions correlated with memory measures among late-onset depressed patients. These results suggest that late-onset depressed patients are more likely to develop cognitive impairment over time than individuals with early-onset depression. Hickie et al.[53] showed reduced hippocampal volumes in older people with both early- and late-onset depression. These reduced hippocampal volumes were associated with deficits in visual and verbal memory performance. Some studies, however, failed to find such changes.[54,55]

Not only in late-life depression, but normal aging also causes changes in hippocampal structure and, thus, altered neural plasticity (reviewed in von Bohlen und Halbach[56]). For example, many studies have shown reduced hippocampal volume during normal aging,[57–59] which may be due to hippocampal atrophy, neuronal loss, a decrease in neuronal densities,[60] or even apoptosis.[61] Interestingly, these changes are related to behavioral deficits in hippocampus-dependent learning and memory.[62] In addition, decreased spine densities of basal and apical dendrites of the CA1 hippocampal area in aged rats[63] and a correlation in the decrease in the densities of basal dendrites in the CA1 area and impairment in spatial learning[64] have been reported.

BDNF: A Key Molecule in Structural and Neural Plasticity

Neurotrophins are growth factors that are critical in regulating structural, synaptic, and morphological plasticity and in modulating the strength and number of synaptic connections and neurotransmission.[65] In addition, the role of neurotrophins in the adult central nervous system is crucial because they participate in the maintenance of neuronal functions, the structural integrity of neurons, and neurogenesis in adult life,[66] suggesting their biological role during the entire life span.

Neurotrophins are homodimeric proteins and are categorized into four different classes: nerve growth factor, BDNF, neurotrophin (NT)-3, and NT-4/5. Most functions of neurotrophins are mediated by the tropomycin receptor kinase (Trk) family of tyrosine kinase receptors. The interaction of neurotrophins with the Trk receptors is specific: Nerve

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growth factor binds with TrkA, BDNF and NT-4 both bind to TrkB, and NT-3 binds to TrkC with the highest affinity but can also bind and mediate its actions via TrkA and TrkB receptors. All neurotrophins can bind to the pan75 neurotrophin receptor ($p75^{NTR}$), which plays a role in neurotrophin transport, ligand-binding specificity, and Trk functioning.[67,68] In addition to the full-length TrkB receptor (TrkB.FL), several noncatalytic truncated TrkB isoforms (TrkB.T1 and TrkB.T2) have also been identified. These truncated TrkBs lack intracellular tyrosine kinase activity[69] and induce signal transduction, resulting in different biological responses.[70] Binding of neurotrophin to the appropriate Trk receptor leads to the dimerization and transphosphorylation of tyrosine residues in the intracellular domain of the Trk receptors and subsequent activation of signaling pathways, leading to altered transcription of critical genes. These signaling pathways include mitogen-activated protein kinase, phosphoinositide 3-kinase, and phospholipase C γ.[71]

The most widely distributed member of the neurotrophin family is BDNF. The *BDNF* gene lies on chromosome 11p13 and encodes pro-BDNF, a precursor peptide of mature BDNF. The *BDNF* gene contains nine 5′ noncoding exons (I-IX) linked to a common 3′ coding exon (IX), producing 22 transcripts.[72] These transcripts facilitate multilevel regulation of BDNF expression and determine the tissue-specific expression.[73] The BDNF is translated as 30- to 35-kDa preproproteins consisting of a preprodomain, a prodomain, and a C-terminal mature neurotrophin domain. The BDNF levels and its intracellular localization in neurons are regulated via several different mechanisms, including BDNF transcripts, messenger RNA (mRNA), protein transport, and regulated cleavage of pro-BDNF to mature BDNF. The pro-BDNF is produced in the endoplasmic reticulum, which is accumulated in the trans-Golgi network via the Golgi apparatus. Pro-BDNF can be cleaved in the endoplasmic reticulum by furin or in the regulated secretary vesicles by proconvertase enzymes. Pro-BDNF binds to sortilin, an intracellular chaperone that binds to the prodomain of BDNF to traffic it to the regulated secretory pathway, in the Golgi apparatus. This facilitates the correct folding of the mature BDNF domain. The mature BDNF domain binds to carboxypeptidase E, thereby sorting BDNF to the regulated secretary pathway.[74] Pro-BDNF can also be processed by serine protease plasmin when pro-BDNF is in the extracellular milieu.[75] A substitution of valine (Val) to methionine (Met) at codon 66 in the prodomain impairs this sorting of BDNF.[76]

The expression of the *BDNF* gene is tightly regulated by neuronal activity, through mechanisms dependent on calcium.[77] The BDNF is present in both pre- and postsynaptic sites and can go under both retrograde and anterograde transport. In addition to BDNF, the function of a receptor for BDNF (i.e., TrkB) is also regulated in an activity-dependent manner. The TrkB is primarily localized in the synaptic sites. Further localization of TrkB occurs at the synaptic sites after neuroanal activity.[74] Neuronal activity, therefore, is critical for synthesis and intracellular targeting of TrkB receptors.[74] Thus, BDNF release and expression of TrkB receptors in a coordinated manner are important for optimal synaptic response.

BDNF is involved in a plethora of biological functions in the brain. More importantly, it is involved in synaptic transmission and maintenance of neuronal plasticity, including regulation of synaptic activity,[78,79] neurite outgrowth, phenotypic maturation, morphological plasticity, and synthesis of proteins for differentiated functioning of neurons and for synaptic functioning. BDNF is also involved in nerve regeneration, neuronal survival, neurite outgrowth, structural integrity, and neurotransmitter synthesis.[80] The role of BDNF has extensively been studied in learning and memory and in cognitive functions. For example, BDNF is necessary and sufficient to induce persistence of long-term memory storage and synaptic consolidation of LTP.[78,81] Behaviorally, BDNF expression increases in the rat hippocampus following behavioral tasks, such as the Morris water maze,[82] the radial

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arm maze,[83] passive avoidance,[84] and contextual fear conditioning.[85] TrkB also plays an important role in such learning and memory because mice over-expressing full-length TrkB show enhanced learning and memory.[86] Thus, a pathological alteration of the BDNF/TrkB may lead to defects in neural maintenance and regeneration and, therefore, structural abnormalities in the brain. This type of alteration may also reduce neural plasticity and, therefore, impair the individual's ability to adapt to crisis situations. Because of the role played by BDNF/TrkB in regulating structural, synaptic, and morphological plasticity, as well as cognition, there has been great interest in their role in the pathogenic mechanisms, particularly MDD. This review focuses on the role of BDNF in stress, aging, and MDD, in general, and during late-life depression, in particular. The role of BDNF in the mechanism of action of antidepressants is also briefly discussed.

Stress and BDNF

An overactive hypothalamus-pituitary-adrenal (HPA) axis has been well established in stress, which leads to chronic elevation of adrenal glucocorticoid production, with impaired negative feedback regulation of the HPA axis.[87] Stress has been shown to be one of the risk factors in late-life depression. O'Brien et al.[88] showed an association between advanced age and increased HPA axis dysregulation in late-life depression. Lee et al.[89] investigated the relationship between the dexamethasone suppression test, cognitive function, depressive symptoms, and hippocampal atrophy in healthy controls, Alzheimer disease patients, and patients with MDD in late life. They found that elevated cortisol was associated with poorer cognitive function across a range of domains, suggesting that HPA axis dysregulation is a risk factor for poorer cognitive performance in older persons. Also pertinent is that older humans with significant prolonged cortisol elevations show a reduced hippocampal volume and deficits in hippocampus-dependent memory tasks and that the degree of hippocampal atrophy strongly correlates with both the degree of cortisol elevation over time and current basal cortisol levels, suggesting that basal cortisol elevation may cause hippocampal damage and impair hippocampus-dependent learning and memory in humans.[90] As discussed earlier, late-life depressed subjects show abnormalities in hippocampal structure, and this could be attributed to depression-related hypercortisolemia. On this basis, Kumar et al. have proposed a model suggesting that prior depressive episodes, aging, stress, and a concomitant release of cortisol and a reduced level of BDNF may cause focal atrophy, which may decrease the threshold for late-life mood disorders, leading to late-life depression.[91]

Although there is no direct evidence showing a relationship to hyperactive HPA axis in late-life depression and BDNF, many preclinical studies suggest a strong relationship of BDNF stress pathophysiological characteristics. The first study showing the role of BDNF in stress was from Smith et al.[92] who showed that immobilization stress in rats lowers the expression of BDNF in the hippocampus, most notably in the dentate gyrus. Subsequently, this was confirmed by other investigators.[93,94] Other stressors, such as social defeat, also decreased BDNF in mouse hippocampus, but interestingly, this decrease extended to cortical and subcortical regions.[95] Because stress is associated with elevated levels of glucocorticoids, several studies have examined the effect of exogenous glucocorticoids on BDNF expression. For example, corticosterone (CORT) treatment in rats reduces BDNF expression in the hippocampus.[92,96] In a recent study, we extensively examined the effects of CORT on BDNF expression in the rat brain and found that CORT decreased expression of BDNF in the hippocampus and in the frontal cortex.[97] Interestingly, adrenalectomy increased the level of BDNF in the hippocampus,[98,99] whereas supplementation of the synthetic glucocorticoid dexamethasone to adrenalectomized rats restored the level of BDNF to normal.[98] These studies suggest that CORT plays a critical role in regulating the synthesis of BDNF.

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We further examined the molecular basis of decreased BDNF synthesis in response to CORT treatment. The rat *BDNF* gene contains four distinct promoters that are linked to four main transcript forms.[100] Although the functions of each BDNF transcript are not clearly known, BDNF transcripts are differentially expressed across brain regions and are differentially regulated.[101,102] When we examined whether a decrease in BDNF expression by CORT is associated with alterations in the expression of a specific BDNF transcript, we found that CORT decreased the expression of selective transcripts II and IV, but not transcript I or III, in the rat frontal cortex and hippocampus.[97] Other studies also suggest that immobilization stress decreased exon IV in the hippocampus[103] and hypothalamus,[104] leading to a decrease in total BDNF expression in these brain areas. Although the functional significance of these changes is yet to be known, it has been shown that exon II has brain-enriched expression patterns, whereas exon IV is widely expressed. Interestingly, exon IV is expressed in the cell body, and is involved in maturation of interneurons through a transsynaptic route.

Because antidepressants can regulate the levels of glucocorticoids[105,106] and they are as effective in early-life depression as in a subpopulation of late-life depressed patients, it is interesting to examine whether glucocorticoid-mediated down regulation of BDNF is reversed by antidepressants and, if so, by what possible mechanism. We showed that desipramine (a norepinephrine blocker) and phenelzine (a monoamine oxidase inhibitor) increased mRNA levels of *BDNF* gene expression in both the frontal cortex and hippocampus, whereas fluoxetine (a serotonin reuptake blocker) increased the mRNA level of BDNF only in the hippocampus.[97] Interestingly, desipramine specifically increased the expression of BDNF transcripts I and III in both the frontal cortex and hippocampus; fluoxetine increased only exon II in the hippocampus; and phenelzine increased exons I and IV in the hippocampus but only exon I in the frontal cortex. Furthermore, all the antidepressants normalized the levels of CORT. When examined, we found that desipramine reversed the CORT-induced decrease in BDNF expression in both the frontal cortex and hippocampus. Fluoxetine only partially reversed such a decrease in the hippocampus, but no effect was found in the frontal cortex. Phenelzine, on the other hand, reversed the CORT-induced decrease in BDNF, partially in the frontal cortex and completely in the hippocampus. Interesting results were noted when individual BDNF transcripts were examined after antidepressant treatment to CORT-implanted rats. We found that all the antidepressants increased mRNA levels of those BDNF transcripts that were affected when the respective antidepressant was given to healthy rats without CORT treatment. For example, desipramine increased exons I and III in the frontal cortex and hippocampus, fluoxetine increased exon II in the hippocampus, and phenelzine increased exon I in the frontal cortex and exons I and IV in the hippocampus. Surprisingly, except for an increase in exon II by fluoxetine in the frontal cortex and in exon IV by phenelzine in the hippocampus, the CORT-mediated decrease in exons II and IV persisted even after antidepressant treatment. Additionaly, despite these different effects of CORT and antidepressants on BDNF transcripts, overall, all the antidepressants increased the level of BDNF mRNA in the brain of CORT-treated rats. Although it is difficult to assess the extent of involvement of a particular exon in the regulation of overall BDNF expression, there is complete reversal by desipramine in both the frontal cortex and hippocampus because the increase in exon III was robust in these brain areas. On the other hand, in the hippocampus, fluoxetine reversed the CORT-mediated decrease of only exon II, but not exon IV; therefore, the reversal was partial. No effect of fluoxetine on total BDNF expression was observed in the frontal cortex, however, because fluoxetine did not increase either exon II or exon IV in the frontal cortex. On the other hand, phenelzine was partially effective in the frontal cortex because of its effects on exon II, but complete reversal was noted in the hippocampus because phenelzine increased the levels of both CORT-decreased exons II and IV. Thus, it appears that antidepressants reverse total BDNF expression in CORT-treated rats; the mechanisms for

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the down regulation of BDNF transcripts by CORT and those that affect their up regulation by antidepressants are different, however.

Recently, in an attempt to identify potential biomarkers for the onset of antidepressant action in patients with MDD, Rojas et al.[107] examined glucocorticoid receptors and serum BDNF levels during antidepressant treatment. Thirty-four depressed outpatients were treated with venlafaxine, and individuals exhibiting a 50% reduction in their baseline Hamilton Depression Rating Scale score by the sixth week of treatment were considered responders. These responders showed an early improvement in parallel with an increase in BDNF levels during the first two weeks of treatment. Nonresponders showed increased glucocorticoid receptor levels by the third week and reduced serum BDNF levels by the sixth week of treatment. The authors concluded that levels of BDNF in serum and glucocorticoid receptor levels in lymphocytes may represent biomarkers that could be used to predict responses to venlafaxine treatment. Whether such a response can be predicted in late-life depression needs to be further investigated.

Lower levels of subjective social support are associated with late-life depression severity[104] and with poorer treatment outcomes[108–112] and an impairment of social support is a risk factor for developing medical and psychiatric illnesses.[110,113] Taylor et al.[114] examined the relationship between the BDNF Val66-Met polymorphism and social support measures in a group of older subjects (aged 60 years or older) composed of 243 with depression and 115 without depression, of whom 233 were Val66 allele homozygotes and 125 were Met66 allele carriers. After controlling for diagnosis and education level, they found that the Met66 allele was associated with lower levels of subjective social support and a trend for fewer social interactions. That study shows that a genetic polymorphism in BDNF may influence social support perception. As previously mentioned, social defeat in mice decreases BDNF not only in the hippocampus but also in cortical and subcortical structures.[95]

Aging and BDNF

In a human postmortem brain study, Webster et al.[115] showed that BDNF mRNA is not altered in the aged hippocampus; they found that expression of full-length TrkB is lower in several subfields of the hippocampus, however, most notably in the subiculum. In the human prefrontal cortex, both BDNF[116] and truncated TrkB (TrkBTK)[117] mRNA levels peak in expression during young adulthood, coincident with the structural and functional maturation of the frontal cortex. Levels of both the full-length form of TrkB mRNA and the truncated form of TrkB decrease over the life span, however. In the temporal cortex, BDNF and truncated TrkB mRNA levels are highest in neonates and decreased with age. In contrast, TrkBTK mRNA levels remained constant across the life span in the temporal cortex.[115]

Neural plasticity is severely affected in aging, suggested by studies showing changes in hippocampal morphology and impairment in LTP.[75,118,119] These studies suggest that a decline in TrkB expression during aging may be critical in lower BDNF functioning and may be causing impaired LTP. Animal studies also suggest that expression of BDNF is not altered during aging in rats.[120–123] In contrary, Hayashi et al.[124] showed that BDNF immunoreactivity declines in cell bodies and dendrites of the neurons in the hippocampus of aged macaque monkeys. Also, the gerbil hippocampus shows an age-dependent decrease in BDNF, which is correlated with memory loss and a decrease of memory.[125] Interestingly, peripheral BDNF changes during aging. For example, Lommatzsch et al.[126] demonstrated that plasma BDNF decreases with an increase in age and that there is a negative correlation between plasma BDNF and age.[127,128] On the other hand, antidepressant treatment to aged rats increases the expression of BDNF in the hippocampus.[129]

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Antidepressants and BDNF

The effects of antidepressants on the expression of the *BDNF* gene have been extensively investigated. In general, when given to healthy rodents, several classes of antidepressants, including monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic agents, noradrenaline reuptake inhibitors, and noradrenergic and specific serotonergic antidepressants, increase the expression of BDNF in the brain.[130–134] Long-term treatment with antidepressants not only increases expression of BDNF in healthy rodents, but also reverses down regulation of BDNF caused by stress.[130,135] These effects are dependent on various factors, however, including length of administration, class of antidepressant, route of administration, age of animal, and doses of the drugs. In general, an increase in BDNF expression occurs after long-term treatment,[130,131,136–138] although short-term treatment with antidepressants has been shown to increase BDNF expression in the cortex.[139] The effects of antidepressants, such as desipramine or fluoxetine, have also been studied in BDNF-deficient mice. These studies show that the behavioral effects of antidepressants are abolished in BDNF-deficient mice,[140] suggesting that BDNF plays an important role in the behavioral effects of antidepressants.

Regulation of BDNF Exons by Antidepressants

To examine how BDNF is regulated in response to antidepressants, we administered different classes of antidepressants to healthy rats and examined whether antidepressants regulate the expression of BDNF via specific BDNF transcript(s).[97] We observed interesting results, such that treatment of healthy rats with desipramine or phenelzine increased mRNA levels of total BDNF in both the frontal cortex and hippocampus, whereas fluoxetine increased the mRNA level of BDNF only in the hippocampus.[97] More interestingly, when we examined the effects of antidepressants on the expression of individual exons containing BDNF transcripts, we found that desipramine specifically increased exons I and III in both the frontal cortex and hippocampus; fluoxetine increased only exon II in the hippocampus; and phenelzine effectively increased exons I and IV in the hippocampus but only exon I in the frontal cortex. In another study, Dias et al.[141] examined the effects of long-term antidepressants on BDNF transcript levels in the rat hippocampus, amygdala, and cortex. They observed that desipramine increased exon III in different cortical areas, whereas fluoxetine had no significant effects on BDNF exons in any of the brain areas studied. Another recent study by Altieri et al.[137] also showed no effect of long-term fluoxetine treatment on BDNF transcripts in the hippocampus. Our observation of increased exon III by desipramine is similar to the findings of Dias et al.[141] but we also noted an increase in the expression of exon I. In addition, contrary to reports by Altieri et al.[137] and Dais et al.[141] we found a selective increase in exon II by fluoxetine in both the frontal cortex and hippocampus. Although some of these discrepancies can be attributed to route of administration or doses of drugs, these findings suggest that there is no unified mechanism for the regulation of BDNF exon(s) by antidepressants and that various classes of antidepressants may affect BDNF exon expression differently.

Antidepressant-Like Effect of BDNF

The role of BDNF in depression also stems from preclinical studies demonstrating that antidepressants regulate the expression of BDNF and BDNF shows antidepressant-like effects in animal models. In a learned helplessness model of depression, infusion of BDNF reduces escape latencies and failure rates in rodents,[142,143] suggesting the effectiveness of BDNF in reducing inescapable random shock–induced depressive behavior. Similarly, intra-midbrain infusion of BDNF in rodents produces an antidepressant-like effect in the forced swim test and learned helpless models of depression.[142] Infusion of BDNF in the dorsal raphe nucleus also resulted in an antidepressant-like effect in the learned helpless model of

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depression.[144] Interestingly, the effects of BDNF on these behavioral paradigms were much longer lasting compared with classic antidepressants.[143,145]

BDNF Abnormalities in Early-Life Depression and Response to Antidepressants

Several studies in humans provide evidence that BDNF plays an important role in early-life depression. In an earlier study, Chen et al.[146] showed that the expression of BDNF is increased in the postmortem brain of depressed subjects treated with antidepressants compared with those who were untreated. We also reported decreased expression of BDNF in prefrontal cortex and hippocampus of suicide subjects who had major depression.[147] Kozicz et al.[148] showed decreased BDNF also in midbrain of depressed suicide subjects. These studies have recently been replicated by Thompson et al.[149] who found similar results in hippocampus of depressed subjects. Interestingly, Guilloux et al.[150] for the first time reported reduced BDNF functions in amygdala of female depressed subjects.

Besides postmortem brain studies, many researchers have examined the level of BDNF in serum or platelets of depressed subjects with and without antidepressant treatment. Although the significance of measurement of BDNF in blood cells is unclear at the present time, however, there are studies showing a complete passage of intact BDNF across the blood–brain barrier by a high-capacity and saturable transport system, as well as its efflux from brain to blood.[151] In addition, platelets are the major source of BDNF in serum[152] and it has been suggested that platelets and neurons are developed from a common embryonic precursor in the neural crest.[153] Therefore, there is a possibility that serum BDNF may represent the central nervous system state.[154] This is further supported by the fact that BDNF is neuronal in origin and is expressed highly in brain. Interestingly, platelet BDNF shows similar changes postnately similar to the brain,[155] suggesting that there are parallel changes in the blood and brain levels of BDNF. Karege et al.[155] were the first to compare BDNF levels in the serum of depressed subjects with those in healthy controls. In 15 male and 15 female depressed patients, they found that the BDNF level was significantly lower compared with that in healthy controls. This decrease was negatively correlated with the severity of depression. Recently, the same group of investigators suggested that the decrease in serum BDNF in depressed patients is related to release mechanisms of BDNF because no change was found in the level of BDNF in blood, but serum and platelet BDNF levels were decreased in depressed patients.[156] Since then, several studies have examined BDNF level in these peripheral tissues before and after antidepressant treatment. For example, Gonul et al.[157] Piccinni et al.[158] and Dell'Osso et al.[159] reported decreases in serum BDNF level in depressed patients. BDNF levels were related to both recurrence and severity of depression.[159] On the other hand, Matrisciano et al.[160] examined serum BDNF levels in healthy subjects and depressed patients at baseline and after 5 weeks and 6 months of sertraline, escitalopram, or venlafaxine treatment. They found that the BDNF level was lower in depressed patients and that sertraline increased the BDNF level after 5 weeks and 6 months, whereas escitalopram increased the BDNF level only after 6 months. Venlafaxine did not change the level of BDNF. There was a negative correlation between increase in BDNF level and decrease in Hamilton Depression Rating Scale score. On the other hand, Gonul et al.[157] reported that depressed patients show an increased BDNF level in serum after treatment with a variety of antidepressants for 8 weeks, including venlafaxine, sertraline, fluoxetine, paroxetine, and citalopram. Similarly, increases in the serum BDNF level by amitriptyline after 36 days, paroxetine after 4 or 8 weeks, or venlafaxine after 12 weeks of treatment to depressed patients were reported.[161–163] Not only antidepressants but vagus nerve stimulation, repetitive transcranial magnetic stimulation,[164] or electroconvulsive therapy,[165] administered to depressed patients, also cause an increase in the serum BDNF level.

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Late-Life Depression and BDNF

In elderly women with a remitted depressive episode of unipolar depression, Laske et al.[166] showed significantly decreased BDNF serum levels compared with healthy female controls. In another study, Lee et al.[167] did not find a correlation between serum BDNF level and depression in the elderly population; it was, however, significantly correlated with deterioration of cognitive functions. Shi et al.[168] measured plasma BDNF and tissue-type plasminogen activator (tPA) in those with late-onset geriatric depression before and after 6 weeks of antidepressant treatment compared with control subjects. The tPA is involved in cleavage of pro-BDNF to mature BDNF and, thus, regulates BDNF action.[75,169] The tPA has been implicated in neuronal and cognitive functions, because it mediates stress-induced decline of neuronal and cognitive functions in the mouse hippocampus.[170] Shi et al.[168] found that baseline plasma BDNF and tPA levels were significantly lower in late-onset geriatric depressed patients compared with controls. Also, there was a heightening tendency of plasma BDNF level after antidepressant treatment. Recently, Chu et al.[171] compared the differences in plasma BDNF levels among institutionalized ethnic Chinese elderly participants with major depression, those with subclinical depression, and a nondepressed control group. They found a significantly negative association between age and plasma BDNF in the regression model and noted that plasma BDNF was significantly lower in the major depressive group than in the nondepressive group. The BDNF plasma concentrations in the subclinically depressive group and control group were also significantly different, suggesting that plasma BDNF levels were reduced in ethnic Chinese elderly patients with MDD and in those with subclinical depression. Overall, these studies demonstrate a negative correlation between serum BDNF and late-life depression.

BDNF Polymorphism and Early- and Late-Life Depression

In humans, a common single-nucleotide polymorphism (SNP) at nucleotide 196 within the 5′ pro-BDNF sequence encodes a variant BDNF at codon 66 (Val66-Met). This Met66 variant affects activity-dependent BDNF secretion.[76,172] This is critical for dendritic trafficking and synaptic localization of BDNF because a Val66Met polymorphism reduces activity-dependent secretion of BDNF, without any change in the level of total BDNF.[173] More interestingly, mice carrying the BDNF Met/Met or Val/Met allele show a reduced hippocampal volume and BDNF Met/Met knock-in mice have reduced dendritic arbor complexity.[174] These studies are relevant to MDD in relation to observed structural abnormalities, including reduced hippocampal volume, which increases the risk for MDD.[175,176] Recently, Frodl et al.[177] examined the effect of the BDNF Val66Met polymorphism on hippocampal and amygdala volumes in patients with depression and in healthy control subjects, and found that MDD patients had significantly reduced hippocampal volumes. They also found smaller hippocampal volumes for depressed patients and for healthy controls carrying the Met-BDNF allele when compared with subjects homozygous for the Val-BDNF allele. No significant difference in amygdala volume was found between depressed patients and healthy controls, and no significant main effects for the BDNF Val66Met polymorphism were observed. They concluded that the Met-BDNF allele carriers might be at risk of developing smaller hippocampal volumes and might be susceptible to MDD. Interestingly, magnetic resonance imaging studies in healthy subjects showed that Val/Val homozygotes had a larger hippocampal volume than Val/Met heterozygotes.[178,179] People with the Met allele also have poor hippocampal-dependent memory function and hippocampal hyperactivation during learning,[76,180] which could be associated with hippocampal hypersensitivity to stress. The direct role of the BDNF Val66Met polymorphism in cognitive impairment comes from a study by Miyajima et al.[181] who investigated six haplotype-tagging SNPs using a cohort of elderly individuals. They found that the presence of the Met allele reduced cognitive performance, suggesting that the

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Met allele is associated with reduced cognitive functioning. The magnetic resonance imaging data showed that the left and right sides of the hippocampus were 5.0% and 3.9% smaller, respectively, in those possessing the Met allele. On the other hand, Kleim et al.[182] demonstrated that training-dependent increases in the amplitude of motor-evoked potentials and motor map reorganization are reduced in healthy subjects with a Val66Met polymorphism in the *BDNF* gene, compared with subjects without the polymorphism. These results suggest that BDNF is involved in mediating the experience-dependent plasticity of the human motor cortex. Furthermore, the Val66Met polymorphism in the *BDNF* gene modulates human cortical plasticity and the response to transcranial magnetic stimulation.[183] Because the majority of the polymorphic relationship of BDNF gene and hippocampal volume studies are focused on early-life depression, how BDNF polymorphism leads to cognitive decline in late-life depression or whether it leads to depression in elderly is not clear and more longitudinal studies are need to clarify this issue.

Earlier, Tsai et al.[184] studied the *BDNF* gene Val66Met polymorphism in MDD and healthy control subjects. They also examined the association of this polymorphism and 4-week fluoxetine therapeutic response in patients with MDD. They found no significant differences for the genotype or allele frequency of the BDNF polymorphism comparing the MDD and control groups. Furthermore, no significant differences were noted comparing the three genotype groups for depressive-cluster symptoms. A trend to improved 4-week fluoxetine antidepressant response was demonstrated, however, for heterozygous patients compared with homozygous analogs. Similarly, Choi et al.[185] reported that the genotype, allele, and allele-carrier distributions for the Val66Met polymorphism did not differ significantly between patients with MDD and healthy controls; they showed, however, that the Val66Met polymorphism of BDNF was associated with citalopram efficacy, with Met-allele carriers responding better to citalopram treatment.

Recently, Licinio et al.[186] studied novel genetic polymorphisms in the *BDNF* gene and assessed their frequencies and associations with MDD or antidepressant response. They identified 83 novel SNPs (30 in untranslated regions, 4 in coding sequences, 37 in introns, and 12 in upstream regions); three of four rare novel-coding SNPs were nonsynonymous. Association analyses of patients with MDD and controls showed that six SNPs were associated with MDD (*rs12273539, rs11030103, rs6265, rs28722151, rs41282918*, and *rs11030101*), and two haplotypes in different blocks (one including Val66 and 1 near exon VIIIh) were significantly associated with MDD. The 5′ untranslated region SNP, *rs61888800*, was associated with antidepressant response, however.

There have been several studies demonstrating a direct link between late-life depression and BDNF polymorphism. Hwang et al.[187] reported that the BDNF Val66Met genotype distribution was significantly different between geriatric depressed patients and healthy subjects and that there was a significant excess of the Met allele in these patients compared with the control group. Duncan et al.[188] found that the Val/Val genotype was associated with higher scores on the cognitive-affective factor of the Beck Depression Inventory-II scale, and somatic-vegetative factor scores, suggesting an association between the Val/Val genotype and higher levels of depression symptoms. In 245 elderly depressed white subjects and 94 elderly comparison white subjects, Taylor et al.[189] examined allelic differences in the BDNF Val66Met polymorphism in late-life depression. Subjects were dichotomized as either homozygous for the Val66 allele or Met66 allele carriers. They found that depressed subjects were more likely to be Met66 allele carriers than were comparison subjects and that there was no significant relationship between genotype and age of onset, number of episodes, or family history of depression. These results suggest that Met66 allele carriers have almost double the odds of having geriatric depression than do Val66 allele homozygotes. They argued that not finding an association with age of onset or number of

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depressive episodes suggests that presence of the Met66 allele would not predispose a person to an earlier age of developing depression but would increase the risk in context of other genetic risk factors for depression or impairment of hippocampus function. On the other hand, Kanellopoulos et al.[190] reported that elderly depressed BDNF Val/Val homozygotes had significantly higher right hippocampal volumes compared with nondepressed Val/Val subjects. There was no difference, however, between the depressed and healthy nondepressed Met carriers. In addition, depressed Met carriers had an earlier age of onset of depressive illness than Val/Val homozygotes, suggesting that neurotrophic factor production protects against pathophysiological processes triggered by depression in older adults with a later age of onset of depression.

Because white matter abnormalities are often associated with late-life depression, Alexopoulos et al.[191] tested the hypothesis of whether the BDNF (Val/Met) polymorphism influences the remission rate in these patients and whether the relationship between BDNF allelic status to remission is influenced by the presence of white matter abnormalities. They found that BDNF(Met) carriers were more likely to achieve remission than BDNF(Val/Val) homozygotes after 12 weeks of escitalopram treatment. They also found that microstructural abnormalities in the corpus callosum, left superior corona radiata, and right inferior longitudinal fasciculum were associated with a lower remission rate; no significant interactions between BDNF(Val66Met) status and microstructural abnormalities in predicting remission were noted, however. These studies suggest that depressed older BDNF(Met) carriers have a higher remission rate than BDNF(Val/Val) homozygotes, which is not related to microstructural white matter abnormalities. On the other hand, Taylor et al.[192] when examining whether the BDNF Val66Met polymorphism was associated with greater volumes of hyperintense lesions in depressed and nondepressed elderly persons, found that the Met66 allele is associated with a risk factor for geriatric depression, including greater magnetic resonance imaging hyperintense lesion severity. More recently, they examined the relationship between a BDNF polymorphism and antidepressant remission rates in an elderly sample with MDD, while testing for mediation effects of social support and hyper-intensities. At the 3-month evaluation, the BDNF Val66Met genotype was not associated with remission. When not controlling for multiple comparisons, Met66 allele carriers were more likely to be remitted at 6 months, with an odds ratio of 1.82. This effect persisted after controlling for lesion volume and social support, neither of which mediated this relationship. They concluded that the Met66 allele may be associated with increased odds of remission in older subjects, but also with increased time to remission.

In a detailed study, Lin et al.[193] assessed both the primary effects of single loci and multilocus interactions and tested the hypothesis that the *BDNF* and *NTRK2*(*TrkB*) genes may contribute to the cause of geriatric depression independently and/or through complex interactions. They genotyped the *BDNF* gene Val66Met (*rs6265*) polymorphism and four SNPs (*rs1187323, rs1187329, rs1778929*, and *rs1545285*) in the *NTRK2* gene in 155 elderly inpatients diagnosed with major depression and 195 age- and sex-similar control subjects. They found that the genotype distributions of all five SNPs tested were significantly different between depressed patients and control subjects. *BDNF rs6265, NTRK2 rs1187323*, and *NTRK2 rs1778929* were also statistically different in the genotypic tests. In addition, the two-marker haplo-type derived from the *rs1187323* and *rs1187329* polymorphisms demonstrated a significant difference between geriatric depression and control groups according to haplotype distribution. BDNF and NTRK2 interactions were also found in the significant two-, three-, four-, and five-locus gene–gene interaction models, suggesting that the *BDNF* and *NTRK2* genes may contribute to the risk of geriatric depression, independently and in an interactive manner. These studies show a clear link between a BDNF polymorphism and early- and late-life depression and response to antidepressant treatment.

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Conclusion and Future Studies

Several preclinical and clinical observations indicate that MDD may be associated with the inability of neural systems to exhibit adaptive plasticity. Given the role of BDNF and its cognate receptors in neural and structural plasticity, and that depression and antidepressants exert opposite actions on BDNF and TrkB expression and functions, it is apparent that BDNF may be crucial in the pathophysiology of MDD and in the mechanism of action of antidepressants. From the studies described in this review, it is clear that both early-onset and late-life depression are associated with altered BDNF expression. In addition, genetic polymorphic studies clearly point out a link between hippocampal volume in these patients as well as cognitive decline, which could possibly lead to depression (Fig. 1). On the other hand, BDNF studies regarding late-onset depression is not well studied and it would be interesting to see whether similar or different pattern of changes in BDNF expression, function, or genetic polymorphism occur in these patients. As far as late-life depression is concerned, it often arises in the context of other chronic medical conditions; social and psychosocial adversity; and aging, which causes changes in the brain and cognition. As discussed earlier, the expression of BDNF and TrkB decline during aging. Thus, future studies need to consider these factors.

Exactly how a decrease in BDNF expression leads to major depression is not clear. Genetic BDNF knock-in and knock-out models could possibly answer this question. Recent studies suggest that a reduction in BDNF level in BDNF heterozygous knockout mice does not produce depression-like symptoms,[194] although overexpression of TrkB reduces anxiety and depressive behavior in mice.[195] Thus, more in-depth studies of the relationship between TrkB and BDNF in major depression are required to answer this question.

There are many avenues in BDNF research in major depression that need further attention. For example, what role does dendritic localization of BDNF/TrkB play in altered plasticity? Recently, it has been shown that BDNF and TrkB can regulate translational machinery in dendrites.[196] Moreover, BDNF induces the expression of Lim kinase 1, a protein kinase whose mRNA translation is inhibited by brain-specific microRNA-134. MicroRNA-134 is localized in dendrites and its overexpression leads to a decrease in spine size through repression of Lim kinase 1 mRNA translation.[197] Thus, studying BDNF/TrkB and other interacting proteins in dendrites will further reveal their novel mechanistic roles in the development of early onset, late life, and late onset depression.

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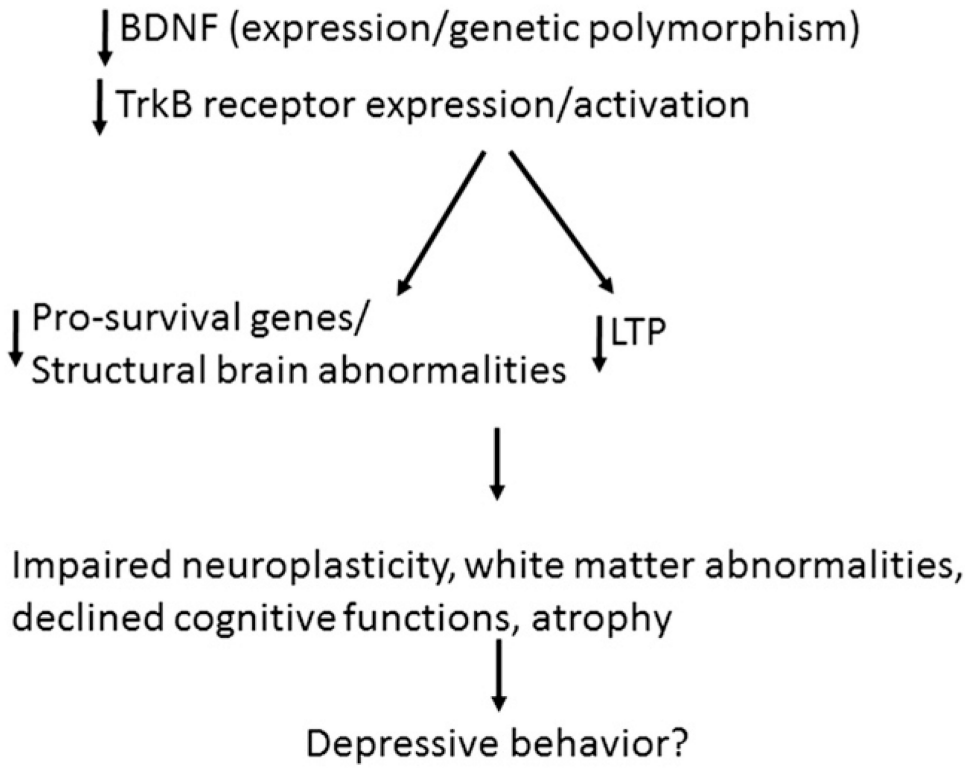

Figure 1. Postulated hypothesis showing role of BDNF in depressive behavior