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Brain-derived neurotrophic factor and inflammation in depression: Pathogenic partners in crime?

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Abstract

Major depressive disorder is a debilitating disorder affecting millions of people each year. Brain-derived neurotrophic factor (BDNF) and inflammation are two prominent biologic risk factors in the pathogenesis of depression that have received considerable attention. Many clinical and animal studies have highlighted associations between low levels of BDNF or high levels of inflammatory markers and the development of behavioral symptoms of depression. However, less is known about potential interaction between BDNF and inflammation, particularly within the central nervous system. Emerging evidence suggests that there is bidirectional regulation between these factors with important implications for the development of depressive symptoms and anti-depressant response. Elevated levels of inflammatory mediators have been shown to reduce expression of BDNF, and BDNF may play an important negative regulatory role on inflammation within the brain. Understanding this interaction more fully within the context of neuropsychiatric disease is important for both developing a fuller understanding of biological pathogenesis of depression and for identifying novel therapeutic opportunities. Here we review these two prominent risk factors for depression with a particular focus on pathogenic implications of their interaction.

Key Words: Brain-derived neurotrophic factor; Microglia; Neuroinflammation; Growth factors; Depression

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Core Tip: Low levels of brain-derived neurotrophic factor (BDNF) and high inflammation have both been implicated as risk factors in the pathogenesis of major depressive disorder. Here we review the role BDNF and inflammation play in the etiology of depression and the interaction between them. Recent evidence suggests a bidirectional connection between these two risk factors: inflammation reduces BDNF expression, and BDNF may have a negative regulatory role in resolving neuroinflammation. Understanding of this interaction in the context of neuropsychiatric disease is important for a fuller understanding of biological pathogenesis of depression and for identifying novel therapeutic opportunities.

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INTRODUCTION

Research has made important advances in recent decades towards the understanding and treatment of major depressive disorder, a debilitating disorder with a heterogeneous range of symptoms. Despite these advancements, depression remains a leading cause of disability with an estimated 264 million individuals worldwide affected by the disorder[1]. In the United States, the economic burden of major depressive disorder is an estimated 210.5 billion dollar[2] with substantial lost productivity and diminished quality of life for affected patients and their families. Recent interest has turned to biomarker and genetic analysis to predict those who may be vulnerable to developing depression and to understand the etiology of patients' existing diagnosis in order to better prevent and treat this debilitating disorder. Two notable biological risk factors for depression are of particular interest: A deficiency in brain-derived neurotrophic factor (BDNF) and inflammation. In this review, we will highlight the mechanisms by which these factors are known to contribute to the development of depression and summarize emerging evidence suggesting that interactions between these two factors within the brain are important in the pathogenesis of depression.

BRAIN DERIVED NEUROTROPHIC FACTOR

BDNF, a member of the neurotrophin family of growth factors, has been well-studied for its role in the pathogenesis of major depressive disorder and antidepressant efficacy. BDNF is a small protein expressed by the *bdnf* gene on chromosome 11 in humans[3]. Transcription of the *bdnf* gene is controlled by nine distinct promoters. The *bdnf* gene contains up to 11 exons; exons II, III, IV, and VII are brain-specific[4]. BDNF is first synthesized as the precursor pre-proBDNF in the endoplasmic reticulum. The pre- domain is cleaved off and proBDNF is transported to the Golgi apparatus. ProBDNF may be secreted in the precursor form or proteolytically cleaved intracellularly or extracellularly to form mature BDNF (mBDNF)[5,6]. Both pro- and mature forms of the BDNF protein are neuroactive, though the activity of proBDNF and mBDNF have largely opposite effects. ProBDNF binds and activates the pan-neurotrophin receptor p75^{NTR}, a member of the tumor necrosis factor receptor family, promoting apoptosis[7]. mBDNF binds with high affinity to the tyrosine kinase receptor tropomyosin receptor kinase B (TrkB).

When mature BDNF, or neurotrophins with lesser affinity for TrkB including neurotrophin-4 and neurotrophin-3, bind to the extracellular domain of TrkB, the intracellular domains of the receptor dimerize and autophosphorylate one of three tyrosine residues. Phosphorylation at each residue initiates a distinct signaling cascade: Ras-PI3K-Akt, Ras-MAP kinase-Erk, or phospholipase C[8]. These signaling cascades activate transcription factors such as CREB, resulting in cell proliferation, cell survival, synaptogenesis, and memory formation (Figure 1).

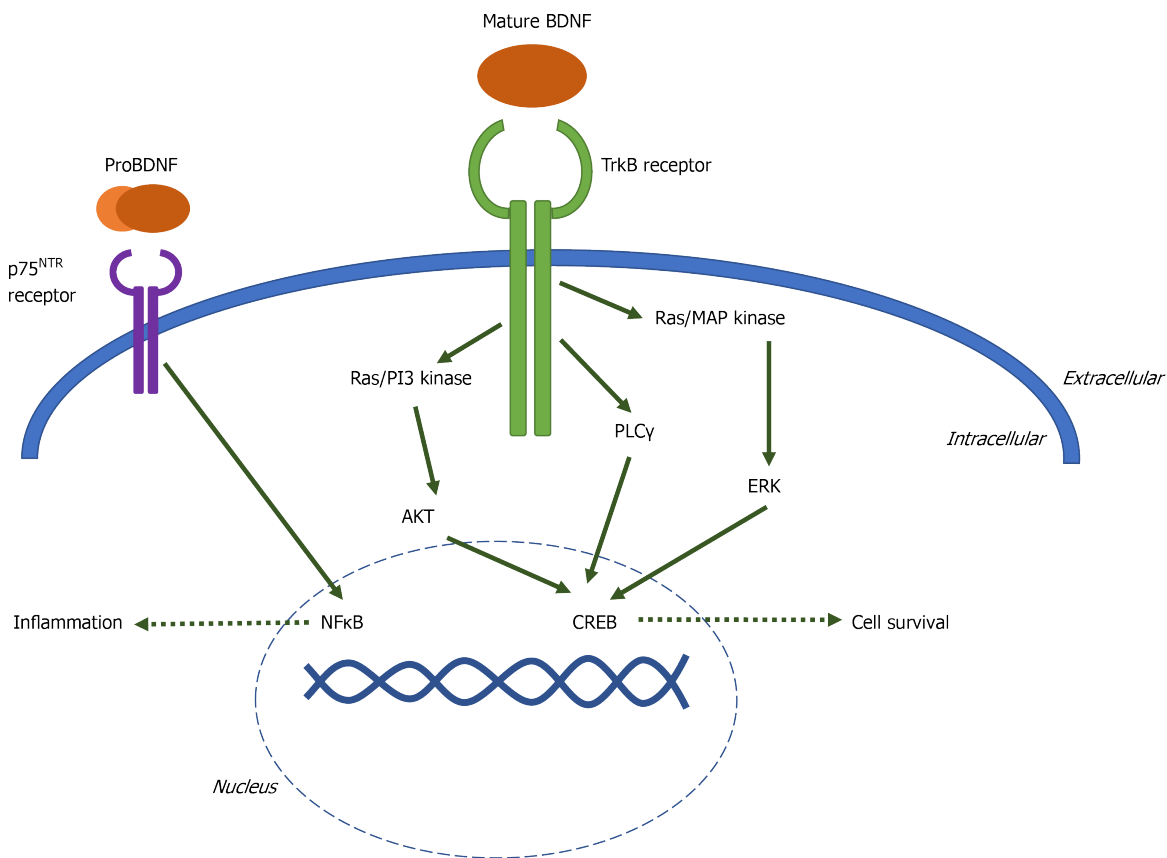


Figure 1 Brain-derived neurotrophic factor signaling cascade diagram. When TrkB is activated by binding mature brain-derived neurotrophic factor (BDNF), the intracellular domains of the receptor dimerize and autophosphorylate one of three tyrosine residues. Phosphorylation at each residue initiates a distinct signaling cascade: Ras-PI3K-Akt, Ras-MAP kinase-Erk, or phospholipase C γ . These signaling cascades activate transcription factor CREB, resulting in cell proliferation, cell survival, synaptogenesis, and memory formation. ProBDNF binds to pan-neurotrophin receptor P75^{NTR}. P75^{NTR} signaling activates transcription factor NF κ B, leading to inflammation and apoptosis. BDNF: Brain-derived neurotrophic factor.

BDNF and TrkB are expressed both peripherally and within the central nervous system. In the periphery, BDNF has been detected in the heart and spleen[9], expressed by myoblasts[10], dorsal root ganglion cells[11], vascular endothelial cells [12], leukocytes[13] and is stored in platelets[14]. In the brain, BDNF is expressed by neurons, astrocytes[15], and microglia[16]. BDNF is highly expressed in the hippocampus and is found in lower concentrations in the cerebral cortex and brainstem[17]. TrkB is expressed in neurons, microglia, and astrocytes throughout the brain[18,19].

A number of factors may modulate BDNF expression or function. Prenatal, early life, social, and unpredictable stress are all associated with reduced BDNF expression or protein levels[20]. Exercise increases BDNF expression[21] and environmental enrichment protects against the effects of stress and early life inflammation on BDNF expression[22,23]. BDNF levels may also decline with age[24,25] and low BDNF levels are associated with age-related neurodegenerative disorders such as Alzheimer's and Parkinson's disease[26,27]. However, some studies suggest BDNF expression does not change with age[28,29].

While a number of genetic factors may contribute to a reduction of BDNF expression or function[30-33], the val66met mutation has garnered considerable attention due to its relevance in psychiatric conditions like bi-polar disorder and suicidality[34,35]. The single nucleotide polymorphism (SNP; rs6265) at nucleotide 196 (G/A) occurs on the 5' pro-BDNF sequence, producing a valine to methionine substitution within codon 66. This SNP does not appear to alter BDNF expression or biological activity, but impairs translocation and activity-dependent secretion[36], thus reducing BDNF- TrkB signaling. The val66met SNP is also associated with reduced serum BDNF protein levels in the periphery[37].

BDNF IN DEPRESSION

The negative correlation between BDNF levels and symptoms of depression have been well established; researchers have been interested in BDNF as a biomarker for depression for decades[38-40]. Clinical data has often demonstrated that patients suffering from major depression disorder are more likely to have alterations in their BDNF-TrkB signaling activity. Numerous studies have found that depressed or suicidal patients have lower BDNF levels than healthy controls[41-48]. Keller *et al*[30] found that suicide victims were more likely to have DNA methylation in the *BDNF* promotor/exon IV compared to control subjects, suggesting a link between epigenetic down-regulation of BDNF and suicidal behavior. Further, psychosocial stress, a known precursor to depression and anxiety, reduces BDNF levels[20].

Genetic analysis reveals several polymorphisms that are associated with susceptibility to developing depression or suicide, such as rs12273363, rs7124442, rs10767664, rs962369, rs908867[31,33]. Of these polymorphisms, the rs6265 SNP known as val66met has been most extensively studied in psychiatric conditions. Some studies suggest that individuals carrying the val66met polymorphism are more vulnerable to developing depression[37,49-52], suicidality[53,54], or to be nonresponsive to antidepressant treatment[55]. However, others dispute this association[55-60]. The val66met polymorphism has been linked to depression in breast cancer patients/survivors[61, 62], but also appears to be protective against chemotherapy-associated cognitive impairments in breast cancer patients[63]. The mixed findings pertaining to association between the val66met SNP and psychiatric disorders suggest that the mutation alone is likely not sufficient to cause pathology. Rather it is a risk factor that interacts with other genetic or environmental factors to contribute to pathogenesis of depression or depressive symptoms.

Clinical studies investigating BDNF have been limited to measuring BDNF in the blood or cerebral spinal fluid, direct measurement of mRNA or protein in the brain being only available in post-mortem tissue samples. However, BDNF does cross the blood-brain barrier (BBB)[64], and Karege *et al*[65] found that brain and serum levels of BDNF are positively correlated in rats. For this reason, measuring peripheral BDNF levels are a feasible indicator of central BDNF expression. Moreover, there is a negative correlation between serum BDNF stored in platelets and depression in humans[66]. BDNF release from platelets may be impaired in depressed patients[67] while antidepressants increase BDNF release from platelets[68], suggesting platelet-derived BDNF is a contributing factor to the interaction between peripheral BDNF levels and depression.

Recent preclinical studies revealed that mice heterozygous for the BDNF allele, which reduces BDNF levels within the brain by about half[69], are susceptible to depressive-like phenotypes after a challenge such as mild stress or acute inflammation [70,71,201]. Direct infusion of BDNF into the rodent brain[72,73] and periphery[74] is protective against the behavioral consequences of stress in the forced swim test and learned helplessness models of depressive-like despair behavior. Further, manipulation of the BDNF-TrkB signaling activity through TrkB agonist 7,8-dihydroxyflavone (DHF)[75] reduces depressive-like behavioral changes induced by social defeat stress [76] and acute inflammation[77]. Many antidepressant treatments increase levels of circulating BDNF[46,68,78-84]. In the brain, anti-depressant treatment induces BDNF mRNA expression in neurons[85], astrocytes[86-88], and microglia[88]. Up-regulation of BDNF may be necessary for the anti-depressant response[89-93].

INFLAMMATION IN THE PERIPHERY AND THE BRAIN

As suggested above, dysregulation in the BDNF-TrkB system may not be a pathological factor that acts alone, rather perturbation within this neurotrophic factor expression/signaling may engender a foundation of vulnerability to subsequent insults to increase the risk of depression or lead to pathology (Figure 2). Inflammation is one risk factor that may well fit this profile.

The ancient Roman encyclopedist Celcus defined inflammation by the presence of “rubor, calor, dolor, tumor”, or redness, heat, pain, and swelling. Modern scientists have a deeper understanding of inflammation as a consequence of the innate immune system’s activation in response to an irritant or loss of homeostatic control due to factors such as stress, obesity, and aging. Acute inflammation occurs when a tissue injury, pathogen, or noxious stimuli is detected. Leukocytes travel to the impacted region to remove the stimuli and repair damage. Chronic inflammation is a persistent

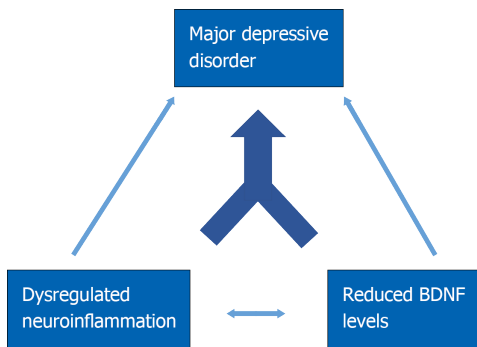


Figure 2 Hypothesis diagram. Brain-derived neurotrophic factor (BDNF) deficiency and elevated or chronic neuroinflammation independently confer vulnerability to development of major depressive disorder. BDNF plays a negative regulatory role in resolving neuroinflammation, and high inflammation reduces BDNF expression. BDNF: Brain-derived neurotrophic factor. BDNF: Brain-derived neurotrophic factor.

and maladaptive response that can be caused by many factors, such as chronic somatic diseases, advancing age, obesity, smoking, and high fat diets. In addition to contributing directly to risk of depression, chronic inflammation may lead to chronic illnesses such as allergies, arthritis, and autoimmune disease that also have high comorbidity with depression.

Invading pathogens or signals released by damaged cells are detected by toll-like receptors (TLR) in the plasma membrane of innate immune cells. TLRs are classified as pattern recognition receptors (PRRs). PRRs recognize and bind pathogen-associated molecular patterns (PAMPs)[94], such as lipopolysaccharide (LPS) on the gram-negative bacterial cell wall, or damage-associated molecular patterns (DAMPs) in a pathogen-independent process known as “sterile inflammation”. Activation of TLRs initiate an intracellular signaling cascade, activating the transcription factor NFκB, causing up-regulation of pro-inflammatory mediators including cytokines, chemokines, cellular adhesion molecules[95], and downstream induction of reactive oxygen species[96]. Of these mediators, macrophage-derived TNFα, IL-1β, IL-6, and IL-10 have received extensive attention due to their roles in regulating the immune system and their effects on the body[97].

Inflammation as a function of the immune response is necessary to protect the life of the organism. Recently, intentional induction of inflammation has been wielded as a promising tool against cancer as immunotherapy[98]. However, numerous studies have shown prolonged and elevated immune activation has significant impacts on physiological, metabolic, and neural/behavioral processes. The effects of peripheral inflammation or immune challenge do not remain in the periphery; inflammatory conditions impact the CNS through several possible mechanisms. The BBB created by the tight junctions of brain endothelium restricts diffusion of pathogens and non-select solutes from the blood into the brain. Peripheral inflammation may disrupt this boundary, increasing the permeability of the BBB and allowing infiltration by circulating monocytes, cytokines, and other substances[99,100]. Cytokines and monocytes attracted by the expression of chemokines such as monocyte chemoattractant protein 1 will travel to the brain and enter through leaky regions of the BBB or through active transport systems. Peripheral cytokines, PAMPs, and DAMPs can also impact brain homeostasis by signaling through the vagus nerve[101] or by signaling through PRRs on the BBB endothelial cells[102,103]. These inflammatory signaling pathways across the BBB initiate the neuroinflammatory response within the brain.

Numerous animal studies have demonstrated that microglia, the resident immune cell in the brain, adopt an “activated” phenotype following peripheral inflammation induced by LPS and live or heat-killed pathogens[100]. In their resting state, microglia are “ramified” with small somas and long highly branched processes. Once microglia detect an immune challenge, their morphology shifts toward an “amoeboid” shape with enlarged soma and shorter, thicker processes. Microglia are the primary source for brain-borne cytokines and other inflammatory mediators.

In addition to producing cytokines, inflammatory microglia also synthesize metabolites of the tryptophan-kynurenine pathway associated with oxidative stress. Tryptophan is converted to kynurenine by the enzyme indolamine-2,3 dioxygenase. Kynurenine metabolism then splits into distinct branches: Kynurenine acid, a metabolite with NMDA receptor antagonist activity, is produced in astrocytes by the enzyme kynurenine aminotransferase, while the enzyme kynurenine monooxygenase (KMO) produces 3-hydroxykynurenine (3-HK) in microglia (Figure 3). 3-HK is further

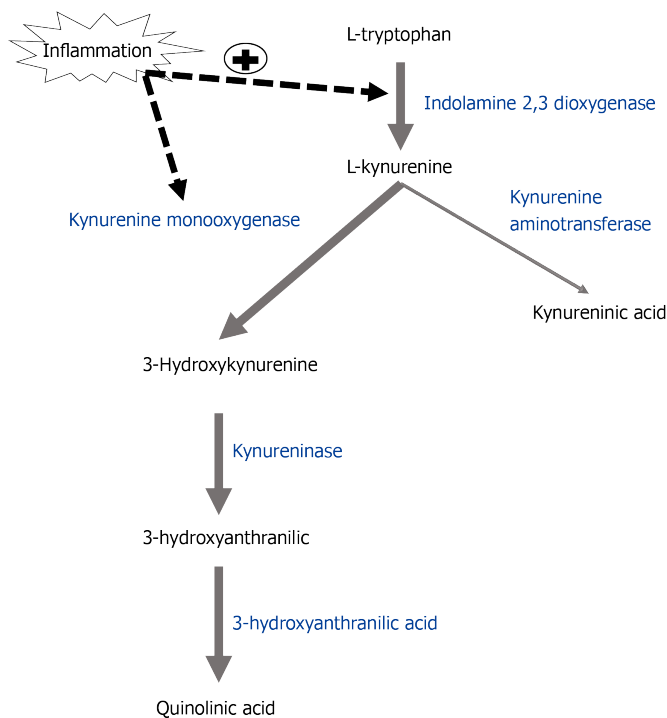


Figure 3 Inflammation shifts kynurenine metabolism pathway towards oxidative stress-associated metabolites. The enzyme indolamine-2,3-dioxygenase (IDO) converts tryptophan to kynurenine. Kynurenine aminotransferase converts kynurenine to kynureninic acid in astrocytes while kynurenine monooxygenase (KMO) metabolizes kynurenine to 3-hydroxykynurenine (3-HK) in microglia. 3-HK is metabolized by kynureninase to 3-hydroxyanthranilic acid and 3-hydroxyanthranilic acid dioxigenase to quinolinic acid. Inflammation up-regulates the enzymes IDO and KMO, resulting in increased levels of KMO-dependent metabolites associated with oxidative stress and depression. IDO: Indolamine-2,3-dioxygenase; KAT: Kynurenine aminotransferase; KMO: Kynurenine monooxygenase; 3-HK: 3-hydroxykynurenine; KYNU: Kynureninase; HAAO: 3-hydroxyanthranilic acid dioxigenase; QA: Quinolinic acid.

metabolized by the enzyme 3-hydroxyanthranilate 3,4-dioxygenase (HAAO) into the neuroactive NMDA receptor agonist quinolinic acid (QA). 3-HK and QA are also free radical inducers and are necessary for the development of inflammation-induced development of depressive-like phenotypes[104], described below.

NEUROINFLAMMATION IN DEPRESSION

Symptoms of typical “sickness behaviors” which cease upon recovery – fatigue, loss of appetite, pain sensitivity, anhedonia, cognitive deficits, social withdrawal – have significant overlap with symptoms of major depressive disorder[105]. In fact, a subset of patients with chronic inflammatory diseases will suffer from longer-lasting symptoms of depression[106]. Individuals suffering from depression but who are otherwise medically healthy often have higher baseline levels of circulating pro-inflammatory mediators, particularly TNF α and IL-6[82,107-110]. Some anti-depressant treatments may reduce neuroinflammation[111,112], but most studies suggest that conventional antidepressants have reduced efficacy in depressed patients who have high inflammation. Conversely, while direct TNF α inhibition was ineffective as an anti-depressant in treatment resistant depression patients with low-moderate CRP levels, it was quite effective in treatment resistant patients with high inflammation[113]. This finding underscores the notion that anti-depressant treatment decisions and efficacy may be improved by integrating understanding of a patient’s inflammatory status. At the cellular/molecular level, post-mortem studies indicate that microglia density in the dorsolateral prefrontal cortex, anterior cingulate cortex, and mediodorsal thalamus[114,115], expression levels of IL-1 β , IL-6, and TNF α in the prefrontal cortex[116,117] and blood[118], and production of QA in the ACC[119] is significantly higher in suicide victims compared to non-suicide controls. Further, anti-depressants with secondary anti-inflammatory properties are more effective in treatment-resistant patients with high baseline levels of inflammatory markers IL-6 and C-reactive protein[120]. These studies suggest a strong association between inflammation and the development of depression.

Inflammation on its own may be sufficient to promote the development of depressive symptoms. Subsets of patients report feelings of depression following cytokine treatment for hepatitis or cancer[121,122]. Experimental treatment with endotoxin[123] or *Salmonella typhi* vaccine in healthy subjects similarly induced symptoms of depression and anxiety alongside acute inflammation[124] and increased kynurenine pathway metabolism. Numerous rodent studies have likewise demonstrated that inflammation can induce depressive-like phenotypes[125].

Inflammation can arise from multiple sources and events. In humans and rodents, acute and chronic stress is known to promote activation of the innate immune system [126,127] and induce microglial activation[115,128]. Psychological stress, a frequent trigger for depression and suicidality in humans, is commonly modeled in rodents using acute or chronic stressors such as social defeat, restraint, or home cage disruption. You *et al*[129] found that rats exposed to chronic mild stress have elevated central and peripheral pro-inflammatory cytokines, reduced neurogenesis in the hippocampus, and display anhedonia-like behavior as measured by the sucrose preference test. Hodes *et al*[109] found that mice with higher baseline levels of circulating IL-6 are more susceptible to developing depressive-like behavioral phenotypes after chronic social stress; IL-6^{-/-} mice were resilient to the effects of social stress. Aging similarly increases vulnerability to neuroinflammation and subsequent depressive-like behaviors. Peripheral LPS treatment promotes a more robust inflammatory responses and sickness behavior in aged mice compared to young adults[130, 131]. Culley *et al*[132] found that LPS increases pro-inflammatory cytokine expression in the prefrontal cortex and impairments in prefrontal cortex-dependent cognition in aged rats. Inflammation associated with obesity[133] and alcohol consumption[134] have similarly been shown to induce depressive symptoms and behaviors in humans and animals.

Researchers have extensively studied depressive-like behavioral changes induced by peripheral immune challenge in rodents[125]. The viral mimetic Poly:IC, attenuated bacterial strain Bacillus Calmette-Guerin (BCG), and LPS are common models used to induce chronic or acute innate immune activation in animal models. Poly:IC increases expression of IL-1 β , TNF α , and CD11b and elevates kynurenine levels in the rat brain, followed by a reduction in saccharin preference up to 72 h after treatment[135]. BCG inoculation induces chronic inflammation, up-regulates TNF α , INF γ , and the tryptophan-kynurenine enzymes IDO and HAAO, and drives despair-like behavior measured by immobility in forced swim test and tail suspension test one week after infection[136,137]. LPS treatment models acute inflammation: Pro-inflammatory cytokine up-regulation and sickness behaviors resolve within 24 h after administration. Once motor activity and food intake is restored at 24 h, mice continue to display anhedonia-like, despair-like, and anxiety-like behavior[131,138,139]. Anti-inflammatory compounds ameliorate the depressive-like behaviors after LPS[138,140-144]. Moreover, many of these effects appear to be dependent on neurotoxic kynurenine metabolism. Inhibition of, or targeted deletion of, the gene for the rate-limiting enzyme IDO prevents development of LPS- and BCG-induced depressive-like behaviors, despite the elevation of pro-inflammatory cytokines[136,145,146]. KMO^{-/-} and HAAO^{-/-} mice are likewise protected against many of the depressive-like behavioral effects of LPS, while direct administration of 3-HK provokes immobility in the tail suspension test and hippocampal-dependent cognitive impairment in the y-maze without an increase in pro-inflammatory cytokines[147], suggesting a causative role of downstream metabolites 3-HK and QA.

However, of the total human population that is exposed to high levels of inflammation, only a relatively small subset goes on to develop symptoms of major depressive disorder. For this reason, researchers have lately turned to investigating the environmental and genetic risk factors that contribute to a patient's vulnerability to developing depression. Recent research has revealed a role for BDNF in modulating the effects of neuroinflammation in a psychiatric context. A deficiency in BDNF may prime the system to develop neuropsychiatric symptoms in a maladaptive response to neuroinflammation-induced sickness behavior (Figure 2).

PATHOGENIC TUG OF WAR?

Mounting evidence has revealed negative correlations between BDNF and neuroinflammation, particularly in psychiatric populations[148,149]. Depression is frequently comorbid with chronic inflammatory conditions, and BDNF deficiency has been identified as a risk factor. Breast cancer survivors are more likely to suffer from inflam-

mation-associated depression if they carry the Met allele in the val66met SNP[62]. BDNF expression is reduced in animals models and patients with rheumatoid arthritis, a disease characterized by chronic inflammation, and associated with major depressive disorders[150]. In Hepatitis C patients undergoing IFN α therapy, elevated cytokine levels are predictive of lower BDNF levels, and both BDNF and cytokine expression are associated with depressive symptoms[151]. Uint *et al*[152] found that elevated levels of both IL-1 β and BDNF were predictive of treatment-resistant depression, but posited that this relationship may be due to the patients' long-term use of anti-depressant medications buoying their BDNF levels. Treating rats with viral mimetic Poly:IC increases expression of IL-1 β , TNF α , IL-6, and CD11b and decreases BDNF and TrkB in the frontal cortex and hippocampus and reduces saccharin preference (anhedonia-like behavior)[135].

Numerous anti-inflammatory treatments have shown promising effects in alleviating depressive-like symptoms and increasing BDNF. Clinically, zinc monotherapy decreases depressive symptoms and increases BDNF in obese subjects[153]. In pre-clinical studies, insulin-like growth factor-1[81] and drugs such as resveratrol[140, 154], imipramine[89,144], doxycycline[144], fluoxetine[155], etazolate[156], chaihushugan-san[157], dihydromyricetin[158], minocycline[159], ketamine[160], and caffeine [161] all inhibit inflammation, increase BDNF, and improve depressive-like behavioral phenotypes.

BDNF activity likewise appears to impact stress or inflammation-induced depression. Mice with genetically reduced baseline levels of BDNF (BDNF^{+/-} mice) develop an exaggerated neuroinflammatory and anhedonia-like response to peripheral LPS challenge compared to wild-type controls[201] and increased despair-like behavior in the forced swim test after acute mild stress[71]. Both the TrkB agonist DHF and the TrkB antagonist ANA-12 are anti-depressant in mice treated with LPS, likely due to opposing effects of BDNF-TrkB activity between the hippocampus and nucleus accumbens[77]. INF α therapy patients with the Val66Met polymorphism display symptoms of suicidal ideation and depression compared to those with the Val allele[162]. Mice with the humanized val66met polymorphism (Val/Met mice) are more sensitive to LPS-induced depressive-like behaviors than Val/Val mice and exhibit microglia with an already primed morphology (unpublished data).

Additionally, investigating the interaction between BDNF-TrkB system and inflammation may be relevant for addressing the sex differences in the presentation of depression. Women report experiencing depression at up to twice the rate of men. BDNF is expressed differentially in various regions of the CNS between males and females and environmental conditions modulate BDNF expression differentially between males and females, although circulating levels of peripheral BDNF appear consistent between sexes[163]. Female BDNF conditional KO mice display more depressive-like behaviors and attenuated anti-depressant response than male BDNF conditional KO mice[164]. Women may also be more vulnerable to developing inflammation-induced depression. Females tend to have higher baseline levels of inflammation than males[165] and have a larger pro-inflammatory and depressive response to endotoxin exposure[166]. In the brain, while male microglia appear to be more reactive early in life than female microglia, female microglia may be reactive and inflammatory later in life, when neuropsychiatric disorders tend to manifest[167]. Estrogen may also play a role: Rodent models of estrogen deficiency results in increased depressive-like behaviors, pro-inflammatory cytokine expression, and increased levels of kynurenine pathway enzyme IDO in the hippocampus[168]. There is also evidence that estrogen regulates expression of BDNF and that the estrogen receptor may be necessary for the protective effects of TrkB activation[163]. These findings suggest the relationship between BDNF, inflammation, and sex warrants further investigation.

BDNF AND NEUROINFLAMMATION: BI-DIRECTIONAL MODULATION

Mounting evidence suggests that the connection between BDNF expression and neuroinflammation regulation is bi-directional in nature (Figure 2). Interestingly, Gomes *et al*[169] found *in vitro* that microglia acutely increase extracellular secretion of BDNF in response to LPS, leading to reduced intracellular levels of BDNF. Cultured human monocyte cells constitutively secrete BDNF, and BDNF secretion is increased when monocytes are stimulated by TNF α or IL-6, although no change in BDNF mRNA was detected[170]. Astrocytes likewise express BDNF when stimulated by TNF α [15] and increase expression of BDNF, TNF α , and IL-6 after LPS treatment[171]. BDNF

regulates proliferation and survival of microglia[172]. This acutely elevated BDNF secretion may be necessary for microglia proliferation and activation after immune challenge[173].

Alternatively, increased BDNF secretion may be a means of inhibitory feedback, as BDNF dampens microglial activation. In spinal cord injury, locally applied BDNF reduces microglial density and inhibits free radical production around injury site [174]. Exogenous BDNF infusion dampens microglial activation by LPS in the substantia nigra in aged mice[175]. In a mouse model of Type I diabetes, overexpressing BDNF in the hippocampus suppressed microglial activation and expression of TNF α and IL-6 induced by hyperglycemia[176]. Further, hypermethylation of BDNF is associated with higher levels of serum IL-6 in patients with acute coronary syndrome[177]. Exogenous BDNF administration significantly decreases TNF α and increases expression of the anti-inflammatory cytokine IL-10 in rodent models of stroke, multiple sclerosis, and pneumococcal meningitis[178-181]. Along this line, BDNF^{+/-} mice have reduced expression of IL-10 and kynurenic acid levels while 3-HK is increased in the brain compared to wild-type controls following chronic mild stress [182]. After LPS treatment, BDNF^{+/-} mice have increased expression of pro-inflammatory cytokines IL-1 β and TNF α and elevated levels of kynurenic acid and QA[201]. Reduced BDNF after viral mimetic poly:IC treatment is likewise accompanied by a shift in the tryptophan/kynurenic ratio[135]. *In vitro* studies in BV2 microglia by Park *et al*[183] have demonstrated that TrkB activation by the agonist DHF inhibits production of nitric oxide, TNF α , and IL-1 β , and translocation and transcriptional activity of NF κ B. These data suggest a role for BDNF-TrkB activity in modulating and resolving the neuroinflammatory response to immune challenge with implications for the development of the depressive-like behavioral phenotypes (Figure 4).

While BDNF secretion may be acutely increased after immune challenge, long-term BDNF expression is hindered in an inflammatory environment. Patients undergoing INF α treatment have significantly reduced BDNF levels[151,162], and Lotrich *et al*[162] found this effect was largest in those with the Val66Met genotype. In rodents, BDNF mRNA is significantly reduced after peripheral injection of LPS in the hippocampus [184,185], substantia nigra[186], and in the whole brain[161]. Similarly, poly I:C also reduces BDNF expression in the brain[135] and *E. coli* treatment down-regulated BDNF and reduced levels of phosphorylated TrkB receptors in the hippocampus of aged animals[187].

Down-regulation of BDNF may be driven by the pro-inflammatory cytokines IL-1 β . *In vitro* experiments have shown that IL-1 β treatment inhibits the neuroprotective effects of BDNF through the PI3-K and MAPK pathways and activity of the CREB transcription factor[188]. In rodents, exogenous IL-1 β treatment blocks BDNF expression in the hippocampus[189-191], and while BDNF expression was not directly measured, chronic inflammation induced by BCG reduces neurogenesis[192] which is a BDNF-TrkB dependent process and correlate of anti-depressant efficacy.

THERAPEUTIC IMPLICATIONS

BDNF as a treatment target for inflammation-associated depression has its challenges. While BDNF and TrkB ligands do cross the b BBB[64,193], BDNF has opposing effects in different cell types and brain regions. For example, LPS treatment down-regulates BDNF in the hippocampus but up-regulates BDNF in the nucleus accumbens[77]. BDNF and TrkB agonists have anti-depressant-like effects in the hippocampus, but pro-depressive-like effects in the nucleus accumbens; inhibiting TrkB activation is anti-depressant in the nucleus accumbens[77]. Further, peripheral infusion of BDNF induces hyperalgesia[194] which, together with differential regionally-distinct CNS effects, precludes the therapeutic utility of systemic BDNF infusion and flooding the CNS with BDNF or TrkB ligands. However, intranasal ketamine, which was recently approved for anti-depressant use, activates BDNF-TrkB signaling directly in the brain, suggesting that therapeutic strategies that deliver BDNF-TrkB modulators directly to target regions within the CNS could prove efficacious.

Peripheral levels of BDNF and inflammatory markers may be useful as biomarkers for treatment-resistant depression, although this approach also is not without challenge. An ideal biomarker of risk or diagnosis should be reliably sensitive to predicting the disease in an asymptomatic individual and be specific to the disorder in question with little to no overlap with other diseases[195]. While low BDNF and high inflammation markers are frequently measured together in depressed individuals, there are many individuals who meet criteria but report no symptoms of depression,

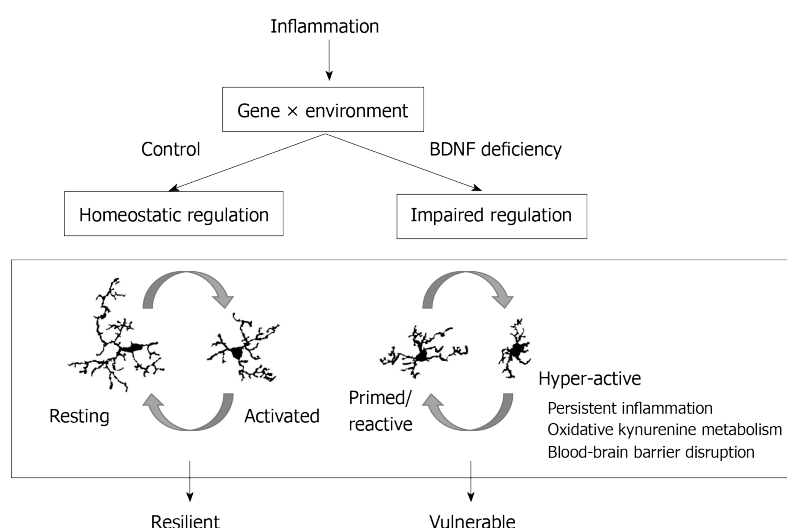


Figure 4 Brain-derived neurotrophic factor deficiency impairs resolution of microglial inflammatory phenotypes. Brain-derived neurotrophic factor (BDNF) levels are altered by genetics and environmental circumstances. Reduced levels of BDNF impair microglia regulation after inflammation. Hyper-active microglia contribute to blood-brain barrier disruption and express higher levels of pro-inflammatory cytokines and kynurenine metabolism pathway enzymes. Individuals with hyper-active microglia are vulnerable to developing symptoms of depression after inflammatory challenge. BDNF: Brain-derived neurotrophic factor.

or become depressed without diverging from average serum levels of each marker. Additionally, low peripheral BDNF and elevated inflammatory markers are reported in other neurodegenerative or neuropsychiatric disorders, including Parkinson's disease, bi-polar disorder, and schizophrenia[196-198]. Epigenetic patterns that disrupt inflammatory homeostasis or functional immunoreactivity of circulating immune cells may provide better prognostic value in predicting vulnerability.

Despite the obstacles, the association between BDNF and inflammation may have utility in deciding treatment options for depressed patients. Patients with inflammation and dysregulation of their BDNF-TrkB system may respond better to anti-depressant drugs with known anti-inflammatory properties, or anti-inflammatory drugs that incidentally have anti-depressant actions, and are able to elevate BDNF levels. Further mechanistic investigations of the interaction between BDNF expression and secretion and pro-inflammatory microglial responses may illuminate potentials targets for novel anti-depressant medication. One emerging approach that has yielded positive results in neurodegenerative disease is to use genetically modified hematopoietic stem cells that express growth factor and traffic specifically to the areas of the brain where pathology occurs[199,200]. While this approach has not yet been tested, it could be viable in cases of severe treatment-resistant depression.

CONCLUSION

Researchers have long recognized BDNF and neuroinflammation as key players in the development of neuropsychiatric conditions, notably major depressive disorder. Recent research has uncovered bi-directional modulation between these two risk factors in the development of depression with promising implications for predicting vulnerability to and treatment of depression. Future studies exploring the mechanisms of BDNF modulation by inflammatory signals, and the anti-inflammatory effects of BDNF in the brain, will provide greater insight into the complex pathogenesis of depression and other neuropsychiatric disorders.

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