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REVIEW

The role of neuroinflammation and neurovascular dysfunction in major depressive disorder

Sang Won Jeon[1]
Yong-Ku Kim[2]

[1]Department of Psychiatry, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, [2]Department of Psychiatry, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, South Korea

Abstract: Although depression has generally been explained with monoamine theory, it is far more multifactorial, and therapies that address the disease's pathway have not been developed. In this context, an understanding of neuroinflammation and neurovascular dysfunction would enable a more comprehensive approach to depression. Inflammation is in a sense a type of allostatic load involving the immune, endocrine, and nervous systems. Neuroinflammation is involved in the pathophysiology of depression by increasing proinflammatory cytokines, activating the hypothalamus–pituitary–adrenal axis, increasing glucocorticoid resistance, and affecting serotonin synthesis and metabolism, neuronal apoptosis and neurogenesis, and neuroplasticity. In future, identifying the subtypes of depression with increased vulnerability to inflammation and testing the effects of inflammatory modulating agents in these patient groups through clinical trials will lead to more concrete conclusions on the matter. The vascular depression hypothesis is supported by evidence for the association between vascular disease and late-onset depression and between ischemic brain lesions and distinctive depressive symptoms. Vascular depression may be the entity most suitable for studies of the mechanisms of depression. Pharmacotherapies used in the prevention and treatment of cerebrovascular disease may help prevent vascular depression. In future, developments in structural and functional imaging, electrophysiology, chronobiology, and genetics will reveal the association between depression and brain lesions. This article aims to give a general review of the existing issues examined in the literature pertaining to depression-related neuroinflammatory and vascular functions, related pathophysiology, applicability to depression treatment, and directions for future research.

Keywords: depressive disorder, neuroinflammation, psychoneuroimmunology, vascular depression, vascular disease

Introduction

Inflammation can be defined as a type of immunoresponse to tissue injuries. In the past, it could only be diagnosed based on visual findings or changes in white-blood-cell counts, but even microinflammation can be measured today using substances released by cells during inflammation, such as cytokines or CRP, as markers. As a result, a considerable amount of research has been directed toward the measurement of the underlying inflammatory changes in several psychiatric disorders, including depression, and the link between physical and mental diseases is being interpreted in relation to inflammation. These efforts have risen from interest in sickness behaviors, such as fatigue and depressive symptoms, which develop in nearly 90% of patients undergoing interferon therapy for hepatitis C or cancer.[1] Initially, investigations focused mostly on the effects of systemic inflammation on the central nervous system (CNS).

Correspondence: Yong-Ku Kim
Department of Psychiatry, College of Medicine, Korea University Ansan Hospital, 123 Jeokgeum-ro, Danwon-gu, Ansan, Gyeonggi 15355, South Korea
Tel +82 31 412 5140
Fax +82 31 412 5144
Email yongku@korea.ac.kr

However, current research also explores neuroinflammation that occurs within the CNS.

The vascular depression hypothesis states that cerebrovascular diseases may be a predisposing or stimulating factor of depression and may cause depression to persist.[2] In other words, the presence of vascular risk factors or vascular diseases per se increases the risk of depression. This theory is supported by epidemiological studies reporting a higher prevalence of depression in patients with hypertension, diabetes mellitus, coronary artery disease, and stroke. Silent cerebral ischemia and white-matter hyperintensity (WMH) are more commonly observed in late-onset depression, and evidence suggests that depressive symptoms are related to the collapse of corticostriatopallidothalamocortical circuits.[3,4]

Such a view of neuroinflammation or neurovascular function in depression addresses the shortcomings of the monoamine theory, the classic pathological model for depression thus far. From this view, depression can be thought of as a result of failure of adjustment to allostatic load, and neuroinflammatory reaction and neurovascular functions are two factors that mediate this. This article aims to give a general review of the issues examined in the literature pertaining to depression-related neuroinflammatory and vascular functions, related pathophysiology, applicability to depression treatment, and directions of future research.

The source of the literature we reviewed was the electronic database Medline (1980–2017). The initial search was for combinations of the following terms: depression/major depressive disorder inflammation/immune/cytokine/neurogenesis/anti-inflammatory/cerebrovascular disease/vascular depression/vascular disease/ischemic. Inclusion criteria were original articles examining immune or vascular mechanisms underlying depression in animal or human subjects, "practice guidelines" for "type of article" from systematic reviews published by PubMed, and articles written in English. Exclusion criteria were letters to editors and editorials without data and studies outside the time window. Based on these criteria, we reviewed the titles of all citations and retrieved relevant abstracts for more detailed evaluation. When there was uncertainty, we studied the full article. We also hand-searched the reference lists of relevant studies and reviews to aid identification of further studies. We identified 965 references of interest, of which 118 were included in this review.

The limitation of this paper is that it is written in the format of narrative review for diverse topics, such as concept, hypothesis, current understanding, and treatment. We may have had certain biases in data-search method and conclusions. However, we used this format to provide a broad overview of a topic-related research area and easy understanding and interpretation.

Stress, cytokines, and depression

Cytokines are a broad and loose category of small proteins (~5–20 kDa) important in cell signaling as inflammatory mediators and they also affect neurotransmitter systems, brain functionality, and mood.[5–7] Although cytokine function itself is not specific to major depressive disorder (MDD), recent research suggests that disease-specific molecular differences within the cytokines might be useful for differentiating patients with MDD from undepressed control subjects (Table 1).[6–16]

Stress is intimately related to the hypothalamic–pituitary–adrenal (HPA) axis and the sympathoadrenal system activated by corticotrophin-releasing hormone (CRH). CRH acts on the CRH_1 and CRH_2 receptors: the former is in charge of the "fight or flight" response, while the latter deals with adjustment to and recovery from stress.[17] When CRH_1 receptors in the paraventricular nucleus of the hypothalamus are activated, the fight-or-flight response occurs, and when CRH_1 receptors in the anterior pituitary are activated, adrenocorticotropic hormone is released, and the adrenal cortex is stimulated to increase synthesis and release of glucocorticoids. Furthermore, CRH stimulates the locus ceruleus to activate the central sympathetic nerve. An acute increase in glucocorticoids, such as cortisol, activates the mineralocorticoid receptors in the pituitary gland and hypothalamus, leading to a reduction in CRH release in a negative-feedback loop. However, exposure to chronic and high-intensity stress continuously increases cortisol secretion, desensitizing the glucocorticoid receptors. In the past, such hypersecretion of cortisol was thought to undermine immune functions, but today hypersecretion of proinflammatory cytokines as a result of activated immune functions is seen as a cause of a continuous rise in cortisol secretion. A

Table 1 Potential biomarkers in peripheral blood for the diagnosis of MDD

Cytokine	Baseline serum level of cytokine in MDD vs controls	Reference(s)
IL6	Increased	6–13
IL10	Reduced	14
IL13	Reduced	15
IL1β	Increased	9
	No significant difference	10
TNF	Increased	8, 10, 12, 16

**Abbreviation:** MDD, major depressive disorder.

previous report suggested that immune cells are not affected by glucocorticoids in depression and chronic stress, because the activation of cytokine pathways, such as p38 MAPK, hinders glucocorticoid signaling.[18,19] In other words, cytokines inhibit the negative-feedback regulation of the HPA axis, maintaining hypercortisolemia. Previous study suggested that an injection of IL1 increases CRH, adrenocorticotropic hormone, and corticosteroid, whereas cytokines, such as IFNα and IL6, increase HPA-axis activity.[19]

Cytokines are also associated with monoamines, such as serotonin, norepinephrine, and dopamine. Recent study findings have suggested that cytokines are involved in serotonin depletion in the CNS. When IL1β, which plays a similar role in stress reactions, is systemically injected, it increases the use of serotonin in the paraventricular nucleus of the hypothalamus and central amygdala, which increases the release of serotonin from the limbic system and norepinephrine from the hypothalamus.[19,20]

Moreover, stress increases proinflammatory cytokines and NFκB in its signaling pathway in the peripheral and CNS, as well as activating microglia in the brain, thereby elevating sensitivity to immunostimulation.[21,22] Brain-derived neurotrophic factor ultimately affects sickness behavior through the growth and development of neurons and synaptic plasticity, and stress-induced IL1 decreases the expression of this protein.[23,24]

Many clinical and experimental studies have proposed the hypothesis that cytokines play an important role in the onset and persistence of depressive symptoms in vulnerable individuals. They suggest that proinflammatory cytokines increase HPA-axis activity and disturb serotonin metabolism and neurogenesis, thereby causing depressive symptoms.[25] Recent studies on the brain–immunity system have presented a few important results pertaining to the association between cytokines and depression as evidence for the cytokine hypothesis of depression (Figure 1).[5,25]

First, the plasma concentration of proinflammatory cytokines is elevated in patients with depression. Studies have reported that plasma IL1, IL6, IL2 receptors, IL6 receptors, and plasma concentrations of acute-phase protein are elevated in patients with MDD.[25,26] Furthermore, there are reports that sensitivity to depression increases in patients with gene polymorphisms for particular cytokines, such as TNFα and IL1.[27,28] Second, the incidence of depression increases in diseases related to inflammatory responses. For example, the incidence of depression increases in cases of *Cytomegalovirus* infection, influenza infection, and chronic hepatitis.[29] Moreover, studies consistently report that autoimmune diseases, such as rheumatoid arthritis and myelosclerosis, and chronic inflammation diseases, such as cancer, are associated with depression.[30] Study findings that administration of cytokine antagonists improves depressive symptoms in depressed
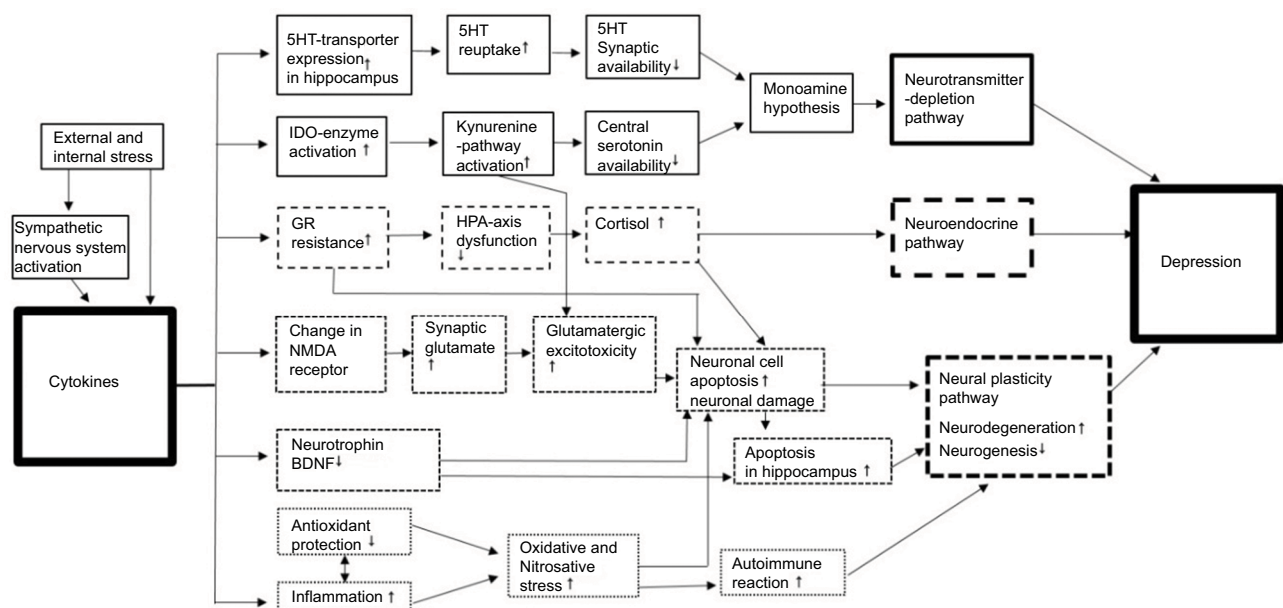
Figure 1 Neuroinflammatory pathways in the pathogenesis of depression.
Notes: Cytokine production is initially activated by stress and sympathetic nervous system activation. In turn, cytokines have an important role by acting via neurotransmitter-depletion, neuroendocrine, and neural plasticity pathways. There are multiple interactions among these pathways, suggesting existence of a complex model for pathogenesis of depression. Reproduced from Jeon SW, Kim YK. Neuroinflammation and cytokine abnormality in major depression: cause or consequence in that illness? *World J Psychiatry.* 2016;6:284–293.[144]
Abbreviations: HT, hydroxytryptamine; BDNF, brain-derived neurotrophic factor; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal; NMDA, *N*-methyl-d-aspartate.

patients with immunoresponses and findings that injection of a trace amount of lipopolysaccharide (LPS; too low to feel physical symptoms) in healthy people induces depression, anxiety, and cognitive impairment serve as evidence.[31,32] Third, regarding the relationship between cytokine-related treatment and depression, at least 25%–50% of patients who are administered IFNα, which is used for patients with such viral infections as hepatitis C or cancer patients, develop depression. Furthermore, behavioral changes, such as depressive mood, anxiety, irritability, apathy, cognitive impairment, fatigue, and pain, have been reported to follow administration of IFNα.[33] Among patients with malignant melanoma receiving IFNα treatment, MDD incidence was reduced more than fourfold, and treatment cessation due to severe depression and neurotoxicity was significantly lower among those who received paroxetine compared to a control group.[34]

Through what mechanism do cytokines affect depression? Cytokines are thought to play an important role in depression through their interaction with monoamines, particularly serotonin, which has the closest relationship to depression. Tryptophan is a key amino acid in serotonin synthesis and is metabolized by IDO. Cytokines, including IL1, IL2, IL6, and IFN, activate IDO, which metabolizes tryptophan, ultimately lowering serum-tryptophan concentration. There are reports that IDO enzymatic activity increases and serum-tryptophan concentration decreases in immunocompromised patients, such as those undergoing immunotherapy and patients with acquired immunodeficiency syndrome, atherosclerosis, and rheumatoid arthritis. In particular, unlike TDO, which is mediated by cortisol, IDO is increased directly by IFNγ and TNFα.[24]

The association between cytokine-induced activation of IDO and depression can also be explained by the kynurenine pathway, which metabolizes tryptophan (Figure 2). There is evidence suggesting that LPS and proinflammatory cytokines increase tryptophan consumption and serotonin turnover in the brain. This is believed to be because cytokine is involved not only in tryptophan deficiency caused by IDO activation but also in the production of neuroactive tryptophan metabolites. Tryptophan is metabolized to kynurenine by TDO and IDO, and kynurenine is in turn metabolized to kynurenic acid (KynA) and 3OH-Kyn. 3OH-Kyn is then metabolized to quinolinic acid (QA). Eventually, QA, a tryptophan metabolite, induces neurotoxicity as an agonist of the *N*-methyl-D-aspartate (NMDA) receptor, while KynA protects the brain from neurotoxicity as an antagonist of the NMDA receptor. In normal situations, KynA is usually produced because astrocytes have an inadequate reserve of enzymes that convert

kynurenine to QA, but during local injuries or inflammation, microglia and macrophage infiltration facilitate QA production and ultimately induce neurotoxicity.[35,36]

Second, the HPA axis is associated with depression. Elevated HPA-axis activity is intimately related to stress, as well as the pathophysiology of depression. Animal studies have reported that CRH injection induces such behaviors as depression and anxiety, sleep disturbance, dietary problems, and reduced activity.[37] Cytokines increase HPA-axis activity by increasing mRNA and the protein of CRH. Moreover, they inhibit the normal negative feedback system of the HPA axis by inducing resistance of corticosteroid receptors in some areas of the brain, such as the hypothalamus and pituitary gland. It has been suggested that these mechanisms through which cytokines affect the HPA axis contribute to the onset of depression.[38]

Third, cytokines may induce depression by altering local brain activity. Neuroimaging findings of patients with depression have shown reduced basal activity in the frontal lobe, temporal lobe, and insula and increased activity in the cerebellum, subcortical structure, and limbic system.[39,40] Of these, the dorsal part of the anterior cingulate cortex (dACC) is an important area that enables individuals to detect physical or social risk and minimize harm by increasing concentration to cope with such risks. Elevated dACC activity increases the risk of affective and anxiety disorders, and it has been confirmed that an IFNα injection increases local blood flow to the dACC on functional magnetic resonance imaging (MRI).[41] Furthermore, a study using ^{18}F positron-emission tomography (PET) reported that IFNα injection affected the activity of the prefrontal cortex and basal ganglia, both of which are associated with fatigue and depressive symptoms.[42,43] Animal studies have also demonstrated that cytokine injection inhibits memory function by affecting the hippocampus.[42]

Neuroinflammation and neurogenesis in depression

Neurogenesis is the creation of new brain cells in adult brains. Considerable evidence supports the view that depression is accompanied by neurodegenerative processes and decreased neurogenesis.[43,44] Chronic stress activates microglia in the brain, and cytokines released by microglia affect neurogenesis. A recent study revealed that neurogenesis may be suppressed or increased depending on the level of microglia activity.[45] This means that microglia have various functions, with some stimulating neurons and others suppressing them. Inflammation and cytokines generally directly suppress neurogenesis. Proinflammatory cytokines, such as TNFα
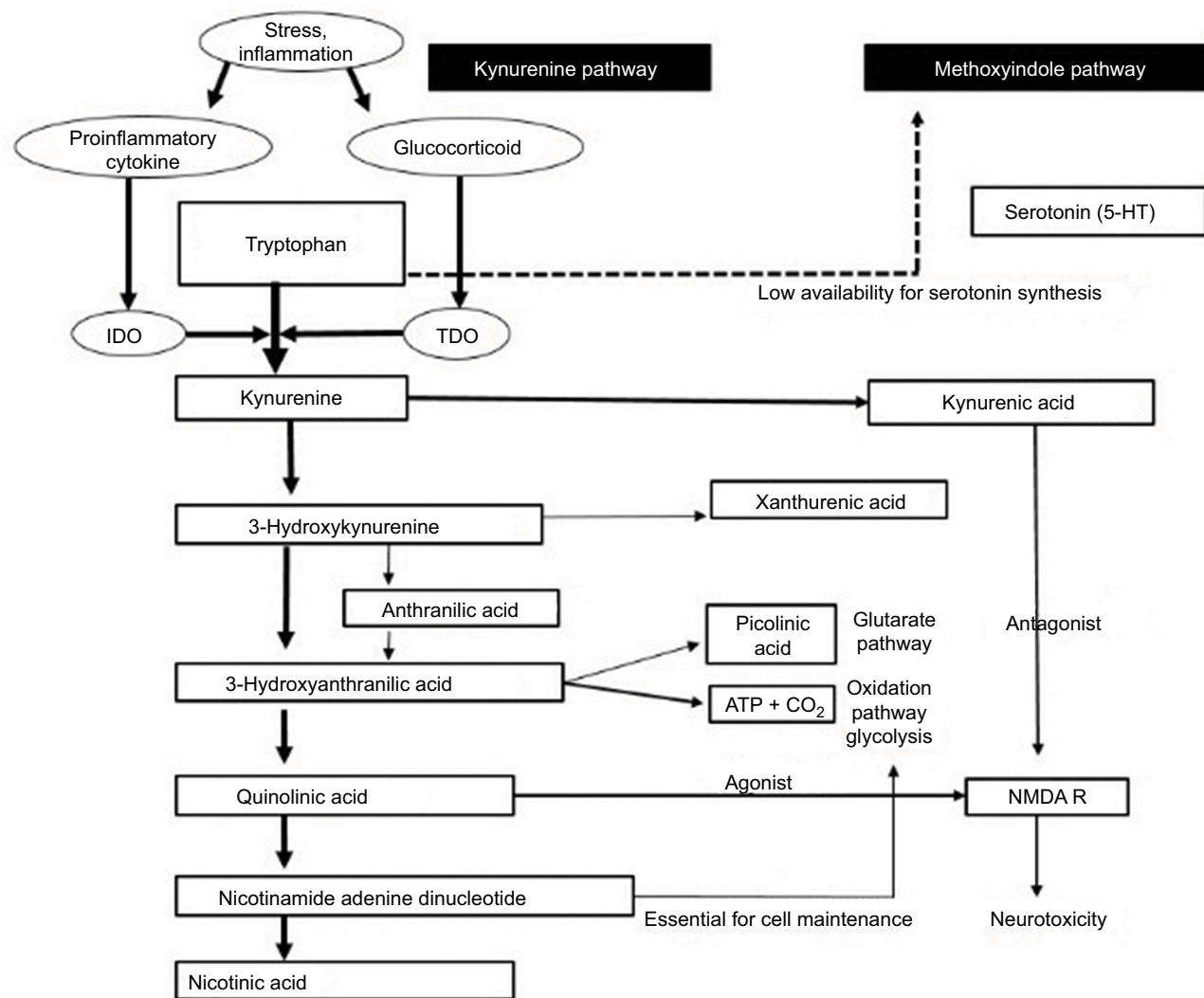
Figure 2 Tryptophan-breakdown metabolic pathway in immunochallenge.
Abbreviations: NMDA R, N-methyl-D-aspartate receptor.

and IFNα, suppress neurogenesis by regulating IL1.[46] In a recent study, inhibiting IL1β activity prevented neurogenesis suppression caused by stress.[47] Meanwhile, administration of drugs that inhibit inflammation leads to recovery or enhancement of neurogenesis.[48] These results support the view that chronic stress stimulates cytokine secretion in peripheral blood and microglia and that cytokines in turn affect neurogenesis.

The neurogenic theory of depression states that impaired neurogenesis is related to the etiology of depression and that successive antidepression therapy would strengthen neurogenesis.[26] Findings that support this theory suggest that stress suppresses neurogenesis, and is a risk factor for depression in vulnerable individuals, patients with depression show cognitive impairment and reduced hippocampal volume

caused by weakened neurogenesis, antidepressants increase neurogenesis and prevent the inhibition of neurogenesis caused by stress, it takes approximately 3–4 weeks for most antidepressants to have an effect, which is equal to the time required for newly produced neurons to mature, and removing the hippocampus – the site for neurogenesis – in animal studies prevents the behavioral effects induced by antidepressant therapy.[26,44] However, hippocampus-volume loss and neurogenesis suppression are not necessarily specific to depression, but are also evident in schizophrenia, dementia, addiction, and anxiety disorders.[49–51] Furthermore, the specific role of neurogenesis in the regulation of depressive symptoms remains unclear. Therefore, some researchers argue that neurogenesis only contributes to cognitive dysfunction, which is common among all the diseases mentioned. However, most

researchers agree that antidepressants increase neurogenesis, which is closely related to mechanisms of antidepressant action.[44] Although it may not be the main cause of depression or an essential factor contributing to the onset of depression, neurogenesis may be a necessary component of effective antidepression therapy. As such, increasing neurogenesis may be a promising strategy for treating depression.[43]

Neuroinflammation, gonadal hormones, and gut–brain axis

Mounting evidence suggests that women are more susceptible to stress-induced depression than males.[52] Stress can disrupt activation of both the HPA and hypothalamic–pituitary–gonadal axes, both of which modulate neuroinflammatory pathways and brain regions involved in depression.[53,54] Therefore, there is a hypothesis that stress differentially alters neuroinflammatory mechanisms associated with depression based on sex.[55,56] Glucocorticoid, estradiol, and progesterone are also known modulators of neuroinflammation.[57] For example, ovariectomy inhibits LPS-induced brain microglial cytokines in mice, whereas estradiol therapy rescues this function.[58]

Gut microbiota have bidirectional interactions with the CNS and immune system, and involve the immune (cytokines), endocrine (HPA axis), autonomic nervous system, and enteric nervous system forming the microbiota–gut–brain axis.[59] Neuroactive substances derived from the intestinal lumen can penetrate the gut mucosa. They are transported by blood, cross the blood–brain barrier, and influence the CNS.[60] It seems likely that gut microbiota play a role in depression through their ability to synthesize or mimic a range of host-signaling immunoactive molecules, such as monoamine and catecholamines.[61,62]

Clinical applications in neuroinflammatory depression

If inflammatory responses contribute to the development of depression, it can be anticipated that anti-inflammatory agents could be therapeutic in depression. Thus far, selective Cox2 inhibitors (eg, celecoxib), nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, tetracycline antibiotics (eg, minocycline), omega-3 fatty acids, and neurosteroids (eg, pregnenolone, allopregnanolone) have been used as supplementary treatments for depression.[63–71] Recently, TNF inhibitors, such as etanercept, have been used as monotherapies for depression,[72] but they have also been used as supplementary therapies with conventional treatment in most studies.

Among these agents, that subject to the most intense research interest has been celecoxib. Small-scale randomized studies have outlined the positive effects of celecoxib on depression.[63] A meta-analysis reviewing 14 clinical trials reported that celecoxib decreased depressive symptoms without the risk of adverse reactions while considerably increasing response rate (OR 7.89, 95% CI 2.94–21.17) and remission rate (OR 6.59, 95% CI 2.24–19.42).[65] However, other NSAIDs had relatively unclear effects, though they were more effective than the placebo.[66] The effects of celecoxib seem to arise from the mechanism in which prostaglandin E_2 synthesis is suppressed while the synthesis of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 and its receptor PPARγ is increased.[67]

In fact, there have been studies showing that adding celecoxib, a Cox2 inhibitor, to conventional selective serotonin-reuptake inhibitor (SSRI) therapy generates better treatment response than SSRI monotherapy.[68,69] Further, supplementary celecoxib therapy for depressive episodes in bipolar disorder has been found to induce earlier treatment responses; acetylsalicylic acid (aspirin) also augmented the effects of the SSRI.[70,71] However, one report found that combining SSRI and NSAIDs undermined antidepressant effects: the effects of citalopram, which normally regulates TNFα and IFNγ in the frontal lobe, were inhibited by ibuprofen in rats.[73] Such laboratory results were also confirmed by data from the STAR*D study, where the proportion of depression-treatment failure was higher among people who took citalopram and AIDs together than among those who took only citalopram.[73,74] However, these results have been rebutted by follow-up studies.[75] Such inconsistency in results should be addressed by establishing a standard for inflammation markers for depression and identifying the subtypes of depression for which AIDs have benefits.

Furthermore, ω3 fatty acids such as eicosapentaenoic acid and docosahexaenoic acid, can be used for rheumatoid arthritis, psoriasis, asthma, and inflammatory bowel disease due to their reduction of proinflammatory cytokines, and they have been effective as a supplementary treatment with antidepressants.[76] Angiotensin-receptor blockers, which are used to treat hypertension, have been found not only to be effective in cardiovascular diseases but also to have anti-inflammatory effects in the CNS.[77] Once their specific mechanism is revealed, they may be used to treat dementia and depression as well. There have been attempts to use IL1ra as a treatment for various mental illnesses, and more recently TNFα has been targeted as a disease-modifying treatment for bipolar disorder.[78] TNFα antagonists, such as adalimumab, etanercept, and infliximab, which have traditionally been used to treat rheumatic diseases, are currently undergoing clinical trials as treatments for depressive episodes in bipolar disorder. It is not yet clear how effective they will be.

A meta-analysis investigating 22 types of antidepressants found that IL-1β and IL-6 decreased in response to treatment and that these results were more evident in SSRI treatment.[79] Antidepressants are thought to regulate cytokines through the effects of cyclic adenosyl monophosphate, serotonin metabolism, the HPA axis, and neurogenesis.[80] Studies have also shed light on the anti-inflammatory effects of riluzole and ketamine, which are glutamatergic modulators. Inflammation increases microglial cell activity while inducing loss of astroglial cells, which will cause the release of glutamates and upregulated NMDA receptors.[81] During this process, riluzole and ketamine prevent neurotoxicity and reduce inflammation by inhibiting glutamate secretion and NMDA receptors. In addition, based on suggestions that CRF receptor antagonists modulate behavioral and endocrine responses to stress, their potential therapeutic efficacy on depression is now being investigated.[82–84] There are enough evidences to show that antidepressant treatment induces a measurable change in the serum level of cytokines (Table 2).[8,16,83–89]

All in all, using anti-inflammatory agents as part of routine treatment for depression would be premature at this point, but selective use in patients for whom inflammation plays a significant role in the course of the disease and in those who are vulnerable to inflammation might have benefits. In such cases, proinflammatory cytokine-receptor inhibitors, antibodies for proinflammatory cytokines, and anti-inflammatory cytokines, as well as the conventional anti-inflammatory agents, may theoretically be used for treatment. In the future, identifying the subtypes of depression with increased vulnerability to inflammation and testing the effects of anti-inflammatory agents in these patient groups through clinical trials will yield more concrete conclusions.

Cerebrovascular disease and depression

Depression is a common complication of stroke.[90] About 20%–50% of all stroke patients experience depression in the first year after a stroke.[91] Studies have argued that depression is associated with cerebral infarction (CI) in particular areas, such as the frontal lobe of the left hemisphere and basal ganglia,[92,93] but subsequent research has reported that the onset of depression is not associated with the site of CI.[94] In one study, investigators argued that the incidence of post-stroke depression varies according to time.[95] They suggested that depression develops with high incidence (25%–31%) within the first month after stroke, but that the incidence of depression declines (16%) about 1–2 years after a stroke. By year 3 after a stroke, they suggested, depression recurs in about 29% of stroke patients who initially suffered from depression. The authors argued that the risk for depression is high within the first month of stroke due to poor physical condition, aphagia, or living alone. Furthermore, 1–2 years after stroke, patients' social relationships are weakened, and by year 3, cerebral atrophy develops, all of which have an important impact on the onset of depression.

A considerable proportion of patients with late-onset depression exhibit silent CI (SCI), which shows no neurologic signs.[96] One study defined cases showing hyperintense lesions greater than 5 mm in nonperiventricular regions as SCI. A total of 22 of 41 patients with late-onset depression had SCI and CNS side effects, such as delirium, akathisia, parkinsonism, and dyskinesia, more common with poorer treatment prognoses in this group of patients than in those without SCI.[97] In another study, SCI was observed in 23% of patients aged ≥65 years, and the radius of the lesions was >3 mm in 79% of these patients.[98] In a postmortem-pathology

Table 2 Potential biomarkers in peripheral blood for antidepressant-treatment outcomes

Cytokine	Serum level of cytokine in MDD vs controls	Results of treatment outcome	Reference(s)
IL6	Baseline increased	Resistant to treatment	83–85
	Increased	Significantly reduced by escitalopram and nortriptyline	86
	—	Escitalopram had no effect	87
	Increased	Fluoxetine had no effect	88
IL11	No known difference	Reduced by escitalopram	87
IL1β	Increased	Significantly reduced by escitalopram and nortriptyline	86
	—	No change with 8 weeks' escitalopram	87
TNF	Baseline increased	Poor response to amitriptyline	8
	Baseline increased	Poor response to SSRIs	16, 89
	Baseline increased	Serum levels negatively correlated with response	84, 89

Abbreviations: MDD, major depressive disorder; SSRI, selective serotonin-reuptake inhibitor.

study, patients who developed late-onset depression had markedly increased cerebral atherosclerosis compared to the normal population.[99] Other studies have also found that WMH on MRI is markedly increased in patients who develop late-onset depression compared to the normal population, which confirms that depression is associated with SCI.[100] Cerebral WMH shown in these patients is associated with extracranial carotid disease, decreased cerebral blood flow, hypertension, diabetes, and heart disease. These findings suggest that cerebrovascular diseases may play an important role in depression.

Neurovascular depression and neurotransmitters

Changes in neurotransmitters that lead to ischemic lesions may be related to depression. Stroke patients with depression have lower 5-hydroxyindolacetic acid levels in their cerebrospinal fluid than those in undepressed stroke patients and normal controls.[101] In a study using PET, $5HT_2$-receptor (a serotonin receptor) binding was found to be elevated in the cortex of the temporal and parietal lobes by 16 months after a left-hemisphere stroke, which could represent receptor upregulation caused by low serotonin levels.[102] In an animal study, norepinephrine levels decreased in the cortex and hippocampus and increased in the striatum and midbrain after ventrolateral ischemic lesion.[103] Some have hypothesized that lesions in the frontal lobe and head of the caudate nucleus may lead to depression, due to damage to the monoamine pathway.[104] An animal study observed elevated dopamine[103] and acetylcholine[105] levels as a result of ischemic lesions, but their roles in depression after a stroke remain unclear.[106] Another animal study confirmed that γ-aminobutyric acid (GABA) uptake was altered after an ischemic injury, and administering a GABA agonist after an ischemic injury had neuroprotective effects.[106] These results suggest that vascular injury of the brain may alter the neurotransmitter system and lead to the development of depression.

Pathophysiology of neurovascular depression

To understand the mechanism of vascular depression, one must consider the location of the lesion, clinical manifestations, age at onset of depression, presence of cognitive impairment, and nonbiological factors. Thus far, two theories have been most frequently cited in the mechanism of vascular depression. The first theory states that lesions that disrupt key brain pathways may be the direct cause of vascular depression. This theory was supported by study findings that lacunar infarcts in the left caudate head or left frontal pole in stroke patients induced depression.[107] However, this theory can only be applied to a small subset of patients who develop depression immediately after a stroke. The second theory suggests that an accumulation of small lesions eventually reaches a threshold that can lead to the onset of depression. In other words, this "threshold" theory hypothesizes the possibility of vulnerabilities caused by wide cerebrovascular disturbances, and it would be the most appropriate theory to explain depression in patients with latent neurologic lesions or those who have suffered a stroke. In clinical studies, neurocognitive function tests conducted on the elderly have revealed deficits in attention and executive function when the total area of WMH exceeded 10 cm².[108] Such cognitive dysfunction was also evident in patients with late-onset depression with vascular risk factors, and these findings support the threshold theory as a mechanism of vascular depression.[109]

Studies investigating the association between the region of white-matter injury and depressive symptoms have consistently found that white-matter injuries in the left frontal lobe are more clearly associated with depressive symptoms than white-matter damage in other areas.[110] Whereas age was significantly associated with deep WMH (DWMH) in the bilateral frontal lobes and left parietal lobe in patients with late-onset depression, age was significantly associated only with DWMH in the bilateral temporoparietal lobes in the study's control group.[95] A clear conclusion has not been drawn on whether DWMH or periventricular WMH (PWMH) are more commonly associated with depression. Based on the vascular depression hypothesis, some studies have suggested a stronger association between depression and DWMH, which are more strongly associated with ischemic damage than periventricular lesions.[111,112] Other researchers have found evidence of an association with both DWMH (frontoparietal) and PWMH and depression,[113] while others have found stronger associations between PWMH and depression.[114,115] The discrepancies in these relationships may be the presence of cognitive impairment, which may be associated both with depressive symptoms and periventricular lesions. Periventricular lesions have been linked to cognitive impairment and ventricular enlargement in several studies of undepressed subjects.[116]

Frontal subcortical circuits originate from the prefrontal cortex and pass through the caudate nucleus, globus pallidus, and dorsomedial thalamus to connect back to the prefrontal cortex. DWMH, a characteristic feature of vascular depression, is speculated to contribute to the onset of depression symptoms through mechanisms involving the injury of these

circuits.[3] Although the cause of WMH is multifactorial, most WMH observed in patients with depression can be explained by cerebral ischemia. In a study that performed postmortem brain-tissue autopsy of 20 patients with late-onset depression and 20 controls, ischemia-induced DWMH findings were present in only a third of the control group, while all patients in the depression group had DWMH induced by ischemia.[117] WMH is not only associated with attention deficit and executive dysfunction but also observed in late-onset depression patients with vascular risk factors.[118] One meta-analysis reported that the OR for WMH was more than four times that of a late-onset-depression group than in an early-onset-depression group.[118]

Diffusion-tensor imaging studies can assess the extent of white-matter injury by measuring fractional anisotropy (FA). These studies have found that elderly with depression show lower FA in the bilateral superior frontal gyri, anterior cingulate cortex, and left-middle frontal gyrus than control groups.[119] Furthermore, one report suggested that patients with late-onset depression had low FA in the right superior frontal gyrus, implying that minimal changes in the white matter of the frontal lobe are related to the onset of depression.[120]

Some have argued that atherosclerosis increases the concentration of inflammatory markers in the blood caused by cerebral ischemia, which in turn stimulates the central monoamine system, inducing neurotoxicity in the monoamine system and ultimately causing depression.[121] In one report, postmortem autopsies of elderly with depression revealed that ICAM1 and VCAM1, which are detected following microvascular disease and ischemia, were significantly elevated in the dorsolateral prefrontal cortex in these individuals.[122]

Clinical applications in neurovascular depression

Many studies have reported that vascular depression does not respond well to antidepressant therapy. WMH observed on MRI was associated with low response to antidepressant treatment.[123] Diffusion-tensor imaging revealed that low response to antidepressant treatment was associated with low FA in various frontal subcortical areas and the limbic system.[124] However, some studies also reported no association between vascular depression and the effects of antidepressant therapy.[125] Furthermore, a study that compared the effects of antidepressants by measuring cerebral blood flow through single-photon-emission computed tomography found that the initial effects of antidepressants increased with decreasing blood flow in the left prefrontal lobe area. This

finding contradicted the existing hypothesis that response to antidepressants would be lower with lower blood flow, ie, when blood circulation is disturbed by ischemic disease.[126]

Meanwhile, some studies have reported that vascular depression was also associated with poor progress and prognosis in addition to poor response to pharmacotherapy.[127,128] In a long-term follow-up study, WMH was related to more chronic progression of depression, and an increase in WMH volume during follow-up was related to poor prognosis of late-onset depression.[94] MRI of patients with severe depression showed that the likelihood of developing vascular dementia was significantly higher during a 6- to 24-month follow-up when WMH was present.[127,129,130] Depressed patients with WMH have also been reported to exhibit more severe disabilities.[129]

Elderly patients with vascular depression have shown a superior remission rate and response to transcranial magnetic stimulation treatment over a placebo group.[130] Furthermore, augmenting antidepressants with calcium-channel blockers for treating vascular depression was effective in reducing depressive symptoms and lowering recurrence rates.[131] Problem-solving therapy was more effective than supportive therapy for achieving remission in depression with executive dysfunction, and the former was also associated with fewer residual symptoms or functional disturbances.[132]

In animal studies, haloperidol, an antagonist of dopamine or σ_1-receptors, prazosin, an antagonist of α_1-adrenergic receptors, clonidine, an agonist of α_2-adrenergic receptors, diazepam, an agonist of GABA, and phenytoin, a voltage-dependent blocker of voltage-gated sodium channels, inhibited recovery of motor function after ischemic injury.[133–137] Meanwhile, amphetamine, an indirect adrenergic agonist, bromocriptine, an agonist of dopamine receptors, and yohimbine and idazoxan, antagonists of α_2-adrenergic receptors, facilitated recovery from an ischemic injury.[133,134] In a study examining pharmacotherapies for poststroke depression, trazodone, nortriptyline, amphetamine, methylphenidate, and selective SSRIs were found to be effective.[135,136] Further research is needed to examine the effects of each antidepressant on the recovery of neurologic deficits in poststroke depression. These studies could shed light on the most appropriate antidepressants for preventing and treating vascular depression.[132–135]

Effective treatment for hypertension and hyperlipidemia lowers cerebrovascular diseases and the subsequent mortality rate.[137] Warfarin and aspirin lowered the risk of stroke in patients with atrial fibrillation. Ticlopidine, aspirin, and dipyridamole reduced the recurrence of stroke in patients who

had suffered ischemic stroke.[138,139] Whether antihypertensive drugs, antihyperlipidemic drugs, and anticoagulants improve the outcomes of depression remains controversial. One study found that using nimodipine, a calcium-channel blocker, with antidepressants for patients with vascular depression improved depression more quickly with lower recurrence and a higher complete remission rate.[140] Other researchers have suggested that antihypertensive drugs themselves should be used with caution, because they increase the incidence of depression, and argued that vascular depression was no exception.[141] Incidence of depression with β-blockers is reportedly higher than with calcium antagonists.[142] In one study, verapamil showed a significant improvement in depressive symptoms, but atenolol did not.[143]

Conclusion

Although depression has generally been explained thus far with the monoamine theory, it is far more multifactorial, and medications that correct the disease pathway have still not been developed. In this context, an understanding of neuroinflammation and neurovascular dysfunction enables a more comprehensive approach to depression.

Inflammation is in a sense a type of allostatic load involving the immune, endocrine, and nervous systems that induces changes in cytokines, the HPA axis, and neurotransmitters. That is, inflammation is involved in the pathophysiology of depression by increasing proinflammatory cytokines, activating the HPA axis, and increasing glucocorticoid resistance, as well as affecting serotonin–norepinephrine–dopamine synthesis and metabolism, neuronal apoptosis, neurogenesis, and neuroplasticity. Therefore, there are continued research efforts to explore neuroinflammation indicators that can be used as depression markers and to investigate the effects of anti-inflammatory medications on depression. However, it is very difficult to establish a consistent indicator amid complex interactions among numerous factors in a tightly knit network and the presence of countless confounding factors. Therefore, it is important to identify the genetic, physiological, and epidemiological characteristics of specific populations vulnerable to inflammatory responses and identify the relevant subtype of depression. Although neuroinflammation cannot yet be deemed a finding specific to depression, it does account for a considerable part of the pathophysiology of depression, and it may be an important factor in certain populations. Moreover, an understanding of neuroinflammatory mechanisms may yield novel depression treatments, suggesting the need for continued research.

Vascular depression may be particularly useful in studying the mechanism of depression. Depending on the site of brain vascular injury, depression can be aggravated, unaltered, or even prevented. Advances in brain imaging, electrophysiology, and chronobiology would enable quantitative measurements of brain lesions, as well as systematic research, such as studies investigating functional changes related to vascular injuries of particular brain areas. The vascular depression theory enables novel therapeutic approaches while laying the foundation for pharmacological studies. Aggressive pharmacotherapy for vascular diseases or vascular risk factors may affect the recovery and prognosis of patients with vascular depression. However, the efficacy of psychotropic medications on vascular depression has not been firmly established, necessitating further research. Investigating depression as an inflammatory and vascular disease will expand our understanding of the relationship between the body and mind and open a new chapter in psychiatry.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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