CME

The roles of neuroinflammation and glutamatergic excitotoxicity in treatment-resistant depression

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ABSTRACT

Major depressive disorder affects nearly 20% of people during their lifetime. A growing body of evidence supports the theory that neuroinflammation plays a prominent role in the neurobiology of depression, which implicates glutamate and gamma aminobutyric acid as key factors in the pathophysiology of the disease process. This article reviews the pathologic pathways of glutamate excess in the central nervous system and how they may be implicated in the underlying disorder of treatment-resistant depression and targeted for treatment.

Keywords: major depressive disorder, treatment-resistant, GABA, neuroinflammation, glutamate, excitotoxicity

Learning objectives

- Understand the limitations of the current monoaminergic model of major depressive disorder.
- Review the cellular biology of glutamate and GABA in the central nervous system, including the effects that glutamatergic excitotoxicity has at the cellular level.
- Understand the link among neuroinflammation, glutamatergic excitotoxicity, and major depressive disorder.
- Explain causes of neuroinflammation.
- Outline pharmacologic therapies that may modulate the effects of glutamate excess in the synaptic cleft.

Major depressive disorder (MDD) affects nearly 20% of people during their lifetime; the 12-month prevalence in the United States is about 10.4%.[1,2] Notably, a large percentage of depression is resistant to treatment with traditional monoaminergic antidepressants, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin-dopamine reuptake inhibitors (SDRIs), and monoamine oxidase inhibitors (MAOIs).[3] Fifty percent to 67% of patients achieve remission with these medications.[4] Patients who have not achieved remission after a trial of two or more traditional antidepressants for 4 to 6 weeks at the maximally tolerated dose are considered to have treatment-resistant depression.[5]

The most significant study to date, Sequenced Treatment Alternatives to Relieve Depression (STAR*D), showed that fewer than 30% of patients treated with traditional serotonergic antidepressants achieved remission with their first antidepressant, and only 50% of patients achieved remission after trying a second medication.[1] Furthermore, patients whose depression did not respond to two different monoaminergic antidepressants had only a 10% to 20% chance of remission with the use of a third medication that uses that same pathway.[6] These data revealed how remarkably ineffective the standard treatment for depression is for a large number of patients.

Taken together, these observations imply that the monoaminergic model of depression does not completely explain the pathophysiology of this disorder. Indeed, it has been proposed more recently that although the monoamines may exert a modulatory influence on the neuropathways involved with depression, they are not the most foundational pathway. Other neurohormones that regulate synaptic transmission in the central nervous system (CNS) may be more influential in the pathology of the disease.[7]

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Key points

- Between 33% and 50% of patients with depression have treatment-resistant depression that does not respond effectively to traditional therapeutics.
- Glutamatergic excitotoxicity refers to the neuronal dysfunction and cell death caused by excessive glutamate release in the brain.
- Neurologic inflammation leads to increased glutamate release in the synapse and can be caused by a variety of physical and psychological factors.
- Using medications that target glutamate release may provide a therapeutic target for patients with treatment-resistant depression.

A growing body of evidence supports the theory that neuroinflammation plays a prominent role in the neurobiology of depression, which implicates glutamate and gamma-aminobutyric acid (GABA) as key factors in the pathophysiology of the disease.[6]

PHYSIOLOGY OF GLUTAMATE

To understand the neuroinflammatory model of depression, a review of glutamate and GABA physiology is necessary (**Figure 1**). In the CNS, glutamate is the principal excitatory neurotransmitter.[6] Once activated, the presynaptic neuron releases glutamate into the synaptic space where it binds to postsynaptic metabotropic receptors and N-methyl-D-aspartate (NMDA) receptors providing an excitatory downstream effect.[8] Elimination of glutamate from the synapse occurs via spillover into the extrasynaptic space or via uptake by astrocytes.[9] Once sequestered inside astrocytes, glutamate is inactivated through conversion into GABA by the enzyme glutamic acid decarboxylase (GAD) or cleaved into inert glutamine.[9] Astrocytes are the primary glial cells that maintain synaptic integrity and remove glutamate from the synaptic space.[9] If glutamate release is extensive enough to overwhelm astrocytic reuptake, then surplus glutamate spills into the extrasynaptic space.[8]

Excessive glutamate release has been shown to contribute to neuronal pathology in three different ways. First, overstimulation of synaptic NMDA receptors on the postsynaptic neuron leads to calcium overload intracellularly. This can lead to cell death via a variety of mechanisms that are beyond the scope of this article.[10]

Second, glutamate that enters the extrasynaptic space has the capability of binding to extrasynaptic NMDA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors, all of which have different effects on neuron health and function.[8] In particular, activation of extrasynaptic NMDA receptors blocks the synthesis and release of brain-derived neurotrophic factor (BDNF); activation of the AMPA receptor may cause an increase in BDNF levels in the postsynaptic neuron.[4,10] BDNF has been widely accepted as a mediator of neuroresilience and a downstream contributor to anxiety and depressive-like behavior as well as an intermediary agent of many classical antidepressant drugs.[4,11] BDNF also has been shown to promote neuroprotection through increased neuroplasticity.[12]

Finally, once in the extrasynaptic space, glutamate can bind to microglial cells, promoting neurotoxicity via further release of inflammatory cytokines, nitric oxide, and additional glutamate, potentiating the risk of overwhelming astrocyte reuptake of excess glutamate.[13] This constellation of effects on the cell has been aptly termed *glutamatergic excitotoxicity*.

NEUROINFLAMMATORY MODEL OF DEPRESSION

The concept of neuroinflammation as a foundational pathway in the pathophysiology of neurologic disease is not new. Neuroinflammation has long been implicated as a cause of other neurologic diseases, such as multiple sclerosis, amyotrophic lateral sclerosis (ALS), and epilepsy.[14] More recently, neuroinflammation has been studied as a pathway for mood disorders and is thought to represent a subtype of depression.[15] Elevated bioinflammatory markers have been found in serum and CNS samples from patients with depression, and neuroinflammation also has been correlated with increased feelings of sadness and anhedonia.[16,17]

Recent studies have shown that inflammatory cytokines in the CNS increase the spillover of glutamate from the intrasynaptic into the extrasynaptic space by decreasing the ability of astrocytes to clear, buffer, and contain glutamate.[15] These inflammatory cytokines bind to astrocytes, which increase oxidative stress and cause impairment of glutamate clearance, contributing to excitotoxicity.[16] Additionally, inflammatory cytokines increase surface expression of glutamate exchange transporters on microglial cells, which leads to increased glutamate extrusion into the extrasynaptic space.[15]

With the advent of MR spectroscopy, studies have found indirect evidence of astrocyte-related glutamatergic dysfunction in the subcortical regions of depressed patients.[14] Postmortem studies suggest that astrocyte dysfunction in relation to glutamate clearance may contribute to the pathophysiology of mood and anxiety disorders.[18] Similar analyses have shown higher levels of glutamate in the cerebrospinal fluid (CSF) of patients with unipolar depression and bipolar disorder.[6] Additionally, glutamatergic abnormalities have been reported in the plasma, serum, CSF, and brain tissue of patients afflicted with mood disorders and obsessive-compulsive disorder.[1,19] Together, these studies indicate that inflammation predictably increases glutamate in the extrasynaptic space.[15]

In proinflammatory states, the increase in glutamate release can be substantial, with extracellular levels of glutamate in the brain increasing up to 100-fold.[20] In the extrasynaptic space, glutamate is able to bind to NMDA receptors, which leads to excitotoxicity and ultimately neuronal damage and death.[19] This glutamatergic excito-

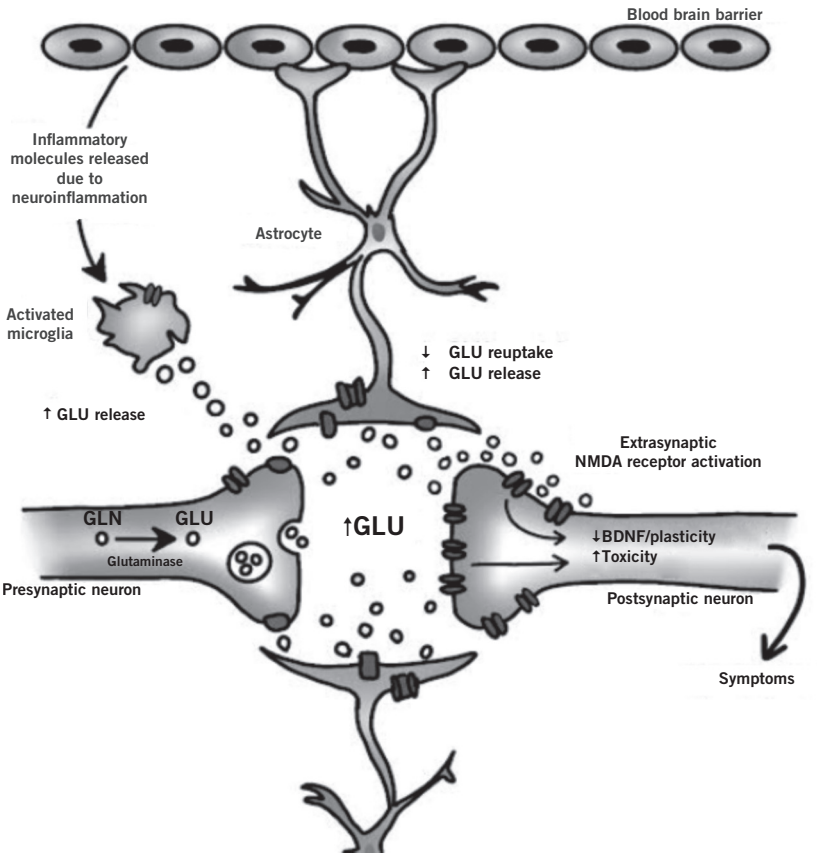

FIGURE 1. The effects of neuroinflammation on glutamate release and activity at the level of the synaptic cleft. Inflammatory molecules present in the CNS increase glutamate release from activated microglia, increase glutamate production in the synaptic neuron, and reduce glutamate reuptake in astrocytes. This leads to increased levels of glutamate in the synapse that then binds to NMDA receptors, causing excitotoxicity in postsynaptic neurons.

Adapted with permission from Haroon E, Miller AH, Sanacora G. Inflammation, glutamate, and glia: a trio of trouble in mood disorders. *Neuropsychopharmacology*. 2016;42(1):193-215.

toxicity leads to reduced BDNF production and increased calcium-mediated neurotoxicity.[10] From these observations, neuroinflammation is proposed as a mechanism of glutamatergic excitotoxicity and a potential pathway for treatment of mood disorders (**Figure 2**).[1,21] In light of this research, altered glutamate neurotransmission in subcortical regions has become a neurochemical target in the development of novel antidepressant medications.[15]

CAUSES OF NEUROINFLAMMATION

Neuroinflammation has many potential causes, including psychosocial stressors, early life adversity, and epigenetic and genetic factors (**Figure 2**).[16] Psychosocial stress has been shown to decrease BDNF production at the transcriptional level, likely through glutamate-mediated pathways.[3] Genetic and epigenetic factors may include T-cell dysregulation.[16] In patients with chronic depression, altered patterns of DNA methylation are seen in astrocytes and microglia, offering a potential pathway for epigenetic regulation.[22] An increased awareness of the intestinal microbiome, diet, and obesity as contributors to neuroinflammation is now understood as well.[16]

Additionally, hypoxia is recognized as a cause of neuroinflammation.[10] In animal models, exposure to high altitude increased glutamate synthesis in 3 to 7 days and was associated with neurodegeneration. However, administration of an NMDA-antagonist ameliorated neuronal degeneration.[23] This implies that chronic hypoxia, including obstructive sleep apnea and chronic respiratory failure, also may lead to neuroinflammation and excitotoxicity. Insomnia alone can even contribute to neuroinflammation, because good quality sleep is associated with a decrease in inflammatory markers such as interleukin-6 (IL-6).[24]

Physiologic stressors, particularly head trauma and ischemia, also have been shown to increase neuroinflammation through an unregulated release of glutamate.[8] After ischemic brain injuries, glutamate accumulates in the intercellular space, acting as a neurotoxin.[25]

Finally, CNS infections and other systemic autoimmune processes have been implicated in neuroinflammation.[26] CNS infections can induce mood changes, such as with pediatric autoimmune neuropsychiatric disorders associated with *streptococcal infections* (PANDAS).[27] Numerous autoimmune disorders have been associated with increased risk of depression, which is hypothesized to involve inflammation from brain-reactive antibodies.[26] In patients with type 1 diabetes, for example, anti-GAD antibodies commonly are elevated in the serum and produce well-known pancreatic pathology, but they also may be implicated in altered glutamate metabolism in the brain.[28] In the CNS, anti-GAD antibodies may reduce the conversion of glutamate to GABA, leading to the accumulation of intracellular glutamate.[29]

THE ROLE OF GABA IN NEUROINFLAMMATION

GABA is the main inhibitory neurotransmitter in the brain.[30] In astrocytes, glutamate is used as the precursor for GABA production and, as such, the two are in chemical equilibrium in the normal steady state.[31] When glutamate levels rise endogenously, GABA also necessarily increases following Le Chatelier principle.[32] Exogenous ingestion of GABA-modulating substances will, therefore, increase glutamate production, which can lead to a neuroinflammatory response. This has been seen in patients with longstanding alcohol use, which reduces endogenous GABA synthesis. During subsequent periods of alcohol withdrawal, the

compensatory decrease in GABA relative to glutamate causes excitotoxicity, which may partially account for alcohol-related brain damage.[30] This may imply that similar effects are likely seen with other GABAergic medications, such as chronic benzodiazepine use (**Figure 3**).

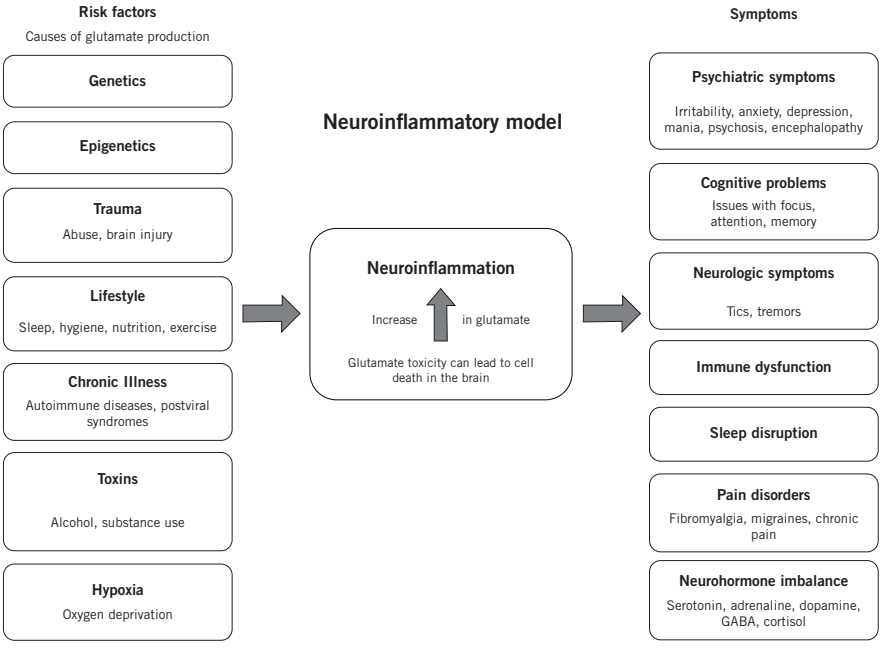

FIGURE 2. Neuroinflammatory risk factors potentially increase glutamate in the synaptic cleft, leading to excitotoxity and, ultimately, symptoms of psychiatric disease

NONPHARMACOLOGIC TREATMENTS

Consider pharmacologic and nonpharmacologic treatments when managing patients with treatment-resistant depression. Medication-assisted treatment for substance use disorders and cognitive behavioral therapy can be offered in addition to standard monoamine-modulating medications. In addition, the clinician should clarify *DSM-5* diagnosis and comorbidities. Between 50% and 60% of patients with treatment-resistant depression eventually are diagnosed with bipolar disorder.[33] Consider reevaluation for manic and hypomanic symptoms. Reducing psychosocial stress also has been proven to help with depression management.[3] Finally, consider sleep apnea and other hypoxic conditions as contributing comorbidities, as discussed earlier.

PHARMACOLOGIC TREATMENT CONSIDERATIONS

In patients whose depression does not respond to traditional monoaminergic antidepressants, glutamatergic excitotoxicty and neuroinflammation are potential targets for treatment. Studies have shown that traditional antidepressants as well as electroconvulsive therapy (ECT) upregulate NMDA expression and AMPA receptor function.[1] Additionally, ECT has been shown to enhance the GAD-mediated conversion of glutamate to GABA in GABAergic neurons, increase BDNF levels in the brain, reduce neuroinflammatory mediators in the CSF, and reduce glutamate levels in the hippocampus.[34] Lithium and valproic acid, classic mood stabilizers, have also been shown to reduce intrasynaptic glutamate levels.[1] These findings suggest that glutamate uptake and metabolism may serve as possible targets for mood and anxiety disorder treatment.[18] Several glutamate-modulating medications should be considered for treatment of treatment-resistant depression, as outlined later.

Lamotrigine is an antiepileptic medication that inhibits voltage-gated sodium, calcium, and potassium channels to inhibit glutamate release presynaptically.[6] This well-known medication has been used for many years to treat epilepsy, its safety is well established, and its cost is nominal. Of all available medications, lamotrigine is thought to have the most direct effect on the glutamate system.[1] Studies have shown benefit with lamotrigine treatment for unipolar and bipolar depression.[6] In these studies, significant reductions in depressive symptoms were seen by 2 months, and significant improvement in social and occupational functioning were seen by 6 months.[6] Of note, patients with more severe illness and longer duration of disease appear to have more significant improvement when treated with lamotrigine.[34] Additionally, studies on ischemic brain injury, hypoxic brain injury, and traumatic brain injury show that lamotrigine also may have neuroprotective effects.[8] Lamotrigine is rapidly absorbed and has bioavailability of 98% when taken orally; peak levels are reached within 3 hours of intake.[24] Concentration in the CNS is nearly equivalent to that of plasma and the drug can be conveniently used in oral form.[24] Unlike most traditional mood stabilizers, lamotrigine is associated with weight loss rather than weight gain.[35] Common adverse reactions include rash and nausea; rare adverse reactions include Stevens-Johnson syndrome, blood dyscrasias, suicidal ideation, and aseptic meningitis.[36] In particular, any unexplained rashes associated with use should be closely monitored.[36]

Ketamine and esketamine are traditional sedatives that have been shown to have remarkable benefits when used in low doses for treatment-resistant depression.[37] These medications are NMDA receptor antagonists and AMPA receptor agonists.[4] They have been shown to increase BDNF production and reduce glutamate release, which are thought to be secondary to these receptor binding actions.[4] Low-dose ketamine (0.5 mg/kg IV) and esketamine (56 to 86 mg intra-

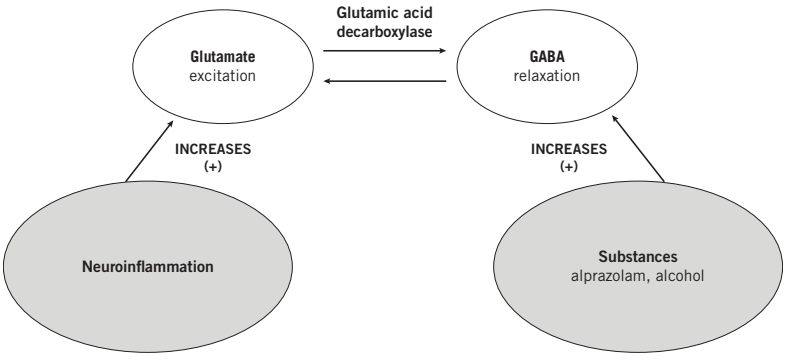

FIGURE 3. The equilibrium between glutamate and GABA. Glutamic acid decarboxylase facilitates the conversion between glutamate and GABA. Exogenous tranquilizers increase GABA receptor activation and neuroinflammation increases glutamate production.

nasally) have been shown to have close to a 75% response rate in patients with treatment-resistant depression within 24 hours and may show benefit as early as 2 hours after administration.[1,37] These medications are increasingly being used for the long-term treatment of treatment-resistant depression and suicidal ideation.[7] Adverse reactions include sedation or dissociation, hypertension, nausea, suicidal ideation, and potential for misuse.[38] Administration of esketamine should be followed by at least 2 hours of patient monitoring.[38]

Topiramate is another well-known medication that acts on the NMDA receptor only.[19] It has shown modest benefit in treating mood and anxiety disorders, is associated with weight loss, has a well-known safety profile, and is inexpensive.[35] However, adverse reactions may limit its use.[19] These include cognitive slowing and drowsiness, renal stone formation, anorexia, suicidal ideation, and (rarely) metabolic acidosis, glaucoma, and hyperthermia.[39]

Riluzole is approved for treating ALS.[40] This drug inhibits glutamate release presynaptically and increases astrocyte uptake of glutamate, which has shown benefit in treating MDD, bipolar disorder, and generalized anxiety disorder.[6] Adverse reactions generally are mild and include nausea, transaminitis, and dizziness.[40]

Memantine is used to treat dementia, and has a downstream regulatory effect on glutamate. Studies of memantine have shown mixed results in the treatment of depression.[19] It may have particular use as an augmentation therapy rather than monotherapy.[1] Adverse reactions include confusion, dizziness, agitation, nausea, and elevated BP.[41]

In addition to these medications, a number of NMDA receptor antagonists are under investigation.[6] Specifically, previously mentioned intranasal esketamine recently received FDA approval for the treatment of treatment-resistant depression and a novel NMDA antagonist labeled MIJ821 was presented at the 2021 American Psychological Association meeting as being "potentially safe and effective for the management of treatment-resistant depression."[38,42]

TABLE 1. Clinical clues to neuroinflammation

Comorbidities
• History of head trauma or brain injury
• History of stroke
• Autoimmune disease (including type 1 diabetes)
• Systemic inflammatory conditions
• Previous CNS infection or systemic infection
• Hypoxia, including obstructive sleep apnea
• History of psychologic or physical trauma
• Drug or alcohol use disorders
Signs and symptoms
• Treatment-resistant depression
• Irritability
• Cognitive symptoms such as difficulties with memory, focus, and attention
• Insomnia
• Selective improvement with benzodiazepines

CONCLUSION

Managing patients with treatment-resistant depression can be a significant challenge. Because traditional monoaminergic medications are rather ineffective for these patients, clinicians must rely on alternatives that act through various other mechanisms of action. In addition to psychotherapy, atypical antidepressants, antipsychotics, and mood stabilizers have all been used. In light of the research reviewed above, the neuroinflammatory model of treatment-resistant depression should also be included in these clinical considerations.

Esketamine, a glutamate modulator, has a specific FDA indication for use in conjunction with an oral antidepressant for treatment-resistant depression.[38] Glutamate-modulating medications should be considered in patients who have comorbidities or histories that may indicate neuroinflammation (**Table 1**). Serum CRP levels also have been studied as potential serum markers for neuroinflammation, but are not considered as sensitive or specific for this pathology.[43]

Although glutamate excitotoxicity may not explain the pathophysiologic mechanism of disease in all patients with treatment-resistant depression, research supports the neuroinflammatory model as a promising target. For patients suffering from chronic, treatment-resistant depression, this presents an exciting new option that can provide significant relief and recovery that has not been achievable through traditional treatment models using monoaminergic medications. **JAAPA**

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