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Glutamate and depression: Reflecting a deepening knowledge of the gut and brain effects of a ubiquitous molecule

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Abstract

The versatility of glutamate as the brain's foremost excitatory neurotransmitter and modulator of neurotransmission and function is considered common knowledge. Years of research have continued to uncover glutamate's effects and roles in several neurological and neuropsychiatric disorders, including depression. It had been considered that a deeper understanding of the roles of glutamate in depression might open a new door to understanding the pathological basis of the disorder, improve the approach to patient management, and lead to the development of newer drugs that may benefit more patients. This review examines our current understanding of the roles of endogenous and exogenous sources of glutamate and the glutamatergic system in the aetiology, progression and management of depression. It also examines the relationships that link the gut-brain axis, glutamate and depression; as it emphasizes how the gut-brain axis could impact depression pathogenesis and management *via* changes in glutamate homeostasis. Finally, we consider what the likely future of glutamate-based therapies and glutamate-based therapeutic manipulations in depression are, and if with them, we are now on the final chapter of understanding the neurochemical milieu of depressive disorders.

Key Words: Brain; Gut microbiome; Mental health; Mood disorders; Neurotransmitters

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Core Tip: The versatility of glutamate as the brain's foremost excitatory neurotransmitter, and modulator of intermediary metabolism in the gastrointestinal tract is considered common knowledge. Years of research suggest glutamate has a role to play in depression. Also, there is increasing evidence of a possible relationship between glutamate and the pathophysiology and/or treatment of depression. The complexity of depression suggests dysregulation of glutamate in sites such as the gastrointestinal tract and brain. The communication link involving dietary glutamate, the gut, endogenous glutamate, and the brain is a multidirectional pathway; the understanding of which is necessary to fully account for glutamate's role in depression.

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INTRODUCTION

Clinical depression or major depressive disorder (MDD) is a chronic, debilitating, and disabling mental health disorder that affects over 300 million people (across all age groups) globally[1-4]. It contributes significantly to the global burden of disease and escalating incidence of suicides amongst teenagers and young adults worldwide. Globally, the prevalence of depression continues to increase[4,5]; with factors such as worsening poverty, increasing unemployment, adverse life events and genetics[4] being recognized as important risk factors for its development.

The discovery of monoamine oxidase inhibitors and tricyclic antidepressants opened opportunities for the treatment of depression and provided insights into the role of neurotransmitters such as dopamine, serotonin and norepinephrine in the pathophysiology of depression[6,7]. However, the shortcomings of the currently-approved pharmacotherapies such as the lag time between the effect of drugs on monoamine availability and their therapeutic effect, inadequate response, and the increasing incidence of treatment-resistant depression[7-9] means that there is still a critical need to better understand the pathophysiology of depression; and develop more-effective and efficient therapeutic interventions for depressive disorders.

The monoamine hypothesis supports the notion that the pathology in depression is primarily depletion in the levels of brain monoamine neurotransmitters including serotonin, norepinephrine, and dopamine[10-12]. In the almost seven decades since its formulation, it has largely explained the symptoms and response to currently available antidepressant therapy. However, inconsistencies in the hypothesis have resulted in further research to better understand depression pathophysiology and management. In the last three decades, there has been compelling clinical[13,14] and preclinical[15,16] evidence demonstrating the involvement of the glutamatergic system in the pathophysiology of depression.

Since the first mention of the glutamate hypothesis of depression in the 1990s[15], our understanding of the versatility of glutamate as the brain's foremost excitatory neurotransmitter, and modulator of neurotransmission and function has increased considerably. Years of research have continued to uncover glutamate's effects and roles in several neurological and neuropsychiatric disorders, including depression. More recently, the antidepressant actions of ketamine, an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist especially in treatment-resistant depression[17,18] was reported; suggesting a deeper understanding of the roles of glutamate in depression could open new doors to understanding the pathological basis of the disorder, improve the approach to patient management, and lead to the development of newer drugs that may benefit more patients. Also, the roles of the gut-brain axis in glutamate signalling have been investigated, with reports that these could also impact the pathophysiology and treatment options in depression[19,20]. This review examines current understanding of the roles of endogenous and exogenous sources of glutamate and the glutamatergic system in the aetiology, progression and management of depression. It also examines the relationships that link the gut-brain axis, depression and glutamate (Figure 1); as it emphasizes how the gut-brain axis could impact depression pathogenesis and management *via* changes in glutamate homeostasis. Finally, we consider what the likely future of glutamate-based therapies and glutamate-based therapeutic manipulations in depression are, and if with them, we are now on the final chapter of understanding the neurochemical milieu of depressive disorder.

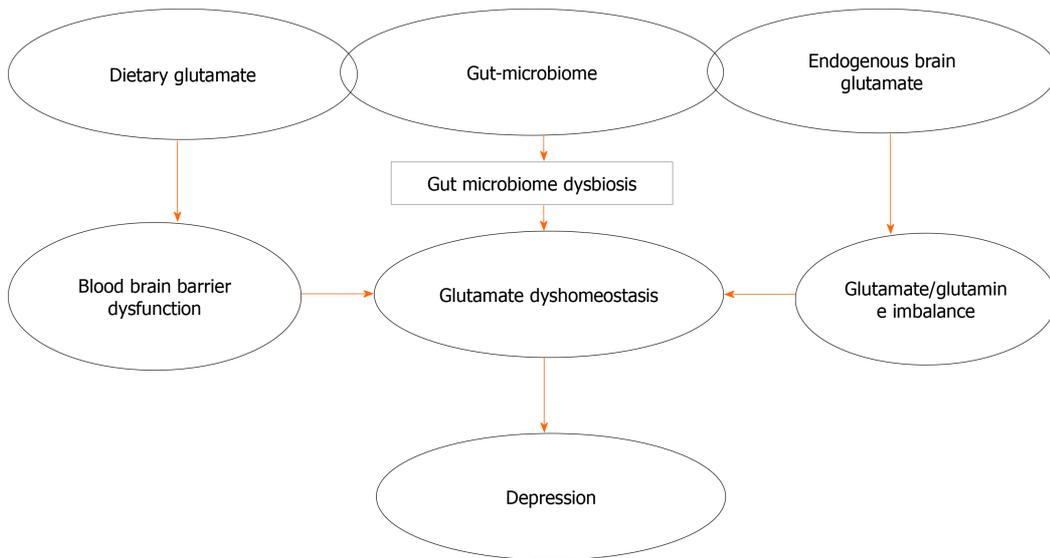


Figure 1 Possible relationships that link dietary glutamate, the gut-brain axis, endogenous glutamate and depression.

GLUTAMATE AND DEPRESSION

Glutamate is an amino acid and the major excitatory neurotransmitter in the brain[21]. In the last few decades, there has been increasing insights into the roles played by the glutamatergic system (Figure 1) in the pathophysiology and treatment of mood disorders generally, and depressive disorders specifically[12,22,23]. Although glutamate is ubiquitous in the brain, excessive release of glutamate has been associated with excitotoxicity-induced brain injury[24]. The possible involvement of the glutamatergic system in mood disorders is supported by preclinical evidence of the antidepressant effects of NMDA antagonists[15,25]. Also, the results of early studies showing alterations in the levels of glutamate (peripherally and centrally) in persons with mood disorders confirmed this involvement[13, 26]. Alterations in excitatory and/or inhibitory neurotransmitters resulting in the alteration of functional connectivity patterns within large brain networks have also been reported[27]. More recently, there is overwhelming evidence of the anxiolytic and antidepressant response to subanaesthetic-doses of ketamine in clinical[27-30] and preclinical studies[31,32].

The ability of diet to cause depression and depression-like phenotypes has been reported[33,34]. Research has continued to show that the consumption of diets rich in fat, deficient in magnesium, or high in monosodium glutamate can cause depression-like behaviours such as decreased social interaction, anhedonia and behavioural despair in rodents[35-37]. While there have been suggestions that these effects are linked to the ability of dietary factors to alter the composition of the gut microbiota [36,37], emerging evidence of the interactions between the gut microbiota and brain neurotransmitters such as dopamine, serotonin, gamma amino-butyric acid and glutamate[9,38] are opening new vistas into possible novel treatment modalities for depression.

Dietary glutamate and depression

Glutamate is an α -amino acid that is useful in the biosynthesis of proteins and important in intermediary metabolism, through its ability to link carbohydrate and amino acid metabolism *via* the tricarboxylic acid cycle[39,40]. Glutamate (in addition to being synthesized in the body in humans) is also derived from dietary sources such as cheese, meat, and several food-seasonings including monosodium glutamate[21,41].

While endogenous brain glutamate has been linked to the pathophysiology of psychiatric conditions such as schizophrenia and mood disorders, the possible role of dietary glutamate (Table 1) in the development of neuropsychiatric conditions is still being evaluated[42]. There have been suggestions that the consumption of diets containing high concentrations of monosodium glutamate could increase body levels of glutamic acid, resulting in hyperglutamatergic neurotransmission, which could possibly contribute to the development of depression[43]. Also, a few studies have reported that factors such as chronic stress that reduce brain levels of glutamate and glutamine causing hypoactive glutamatergic signaling in the mouse prefrontal cortex are also associated with the development of depression[44], suggesting that regarding brain glutamatergic transmission a delicate balance always needs to be maintained.

In the last few years, reports from preclinical studies have associated the use of monosodium glutamate with the development of behavioural phenotypes such as anxiety and depression; and the ability to influence brain endogenous glutamate and glutamatergic neurotransmission[35,42,44-46].

Table 1 Dietary glutamate and depression

Subject	Outcome	Ref.
Human	In non-obese participants, diets high in levels of glutamic acid were associated with greater depression symptomatology	Kumar <i>et al</i> [43]
Adult mice	While chronic immobilization stress decreased sodium-coupled neutral amino acid transporter (SNAT)-1 and 2 in neurons and glutamate transporter (GLT)1, SNAT3, and SNAT5 in astrocytes in the medial prefrontal cortex, glutamine – supplemented diet ameliorated these decrements	Baek <i>et al</i> [44]
Neonatal rats	Subcutaneous injection of monosodium glutamate (MSG) increased the immobility time in the forced swim test and the freezing reaction in the contextual fear conditioning. MSG also increased serotonin uptake in the cerebral cortices and caused deregulation of the hypothalamic-pituitary-adrenal axis	Quines <i>et al</i> [35]
Mice	Anxiolytic and memory-enhancing effects at low doses of MSG; however, at higher doses, anxiety and memory retardation were observed	Onalapo <i>et al</i> [45]
Mice	Higher doses of dietary glutamate resulted in an increase in plasma glutamate and glutamine but no difference in total brain glutamate or glutamine levels	Onalapo <i>et al</i> [21,45,46]
Mice	Anxiolytic response in females, and anxiogenic response in males following dietary MSG. A decrease in behavioural despair was observed in both sexes (females more than males)	Onalapo <i>et al</i> [46,47]
Mice	Anxiogenic effect was observed following subchronic oral administration of MSG	Onalapo <i>et al</i> [49]

There have also been reports from studies that monosodium glutamate could directly influence the concentrations of brain neurotransmitters such as serotonin and glutamate[21,35,45,47], although there have also been reports to the contrary[48].

The relationship between dietary monosodium glutamate and depression has been examined by a few studies[35,43,47]. The results of a clinical analysis that examined the relationship between the consumption of a diet high in glutamic acid and the development of depressive symptoms in a group of persons with schizophrenia revealed that in non-obese patients the consumption of high dietary glutamic acid was associated with an increase in depressive symptoms, although this was linked to the susceptibility of persons with one psychiatric condition to develop other co-morbidities[42]. A preclinical study by Quines *et al*[35] that examined the effects of monosodium glutamate administered parenterally in the neonatal period with exposure to behavioural paradigms on postnatal days 60-64 reported the presence of anxiety and behavioural despair. However, studies from our laboratory revealed that while orally administered monosodium glutamate was associated with the development of anxiety behaviour, especially in male mice[21,45,49], an antidepressant effect was observed in the behavioural-despair paradigms irrespective of sex[47]. The results of these studies from our laboratory suggest that the antidepressant response observed when monosodium glutamate was administered by gavage (compared to the response following parenteral administration) could have been influenced by the gut microbiota or the gut-brain axis, or by the ability of monosodium glutamate (at these doses) to minimally increase brain levels of glutamate which could have antidepressant benefits as previously reported[44].

Endogenous brain glutamate and depression

Glutamate plays an important role in the modulation of synaptic plasticity and transmission. It is also the precursor of the inhibitory neurotransmitter gamma amino-butyric acid (GABA). Studies have shown that dysregulation of glutamatergic transmission or alterations in brain concentrations of glutamate is associated with derangement of brain function, development of excitotoxic brain injury, and cell death[24,47]. There have also been reports showing that alterations in glutamatergic neurotransmission contribute significantly to the development of peripheral and central nervous system disorders[50]. In the last few years, the possible relationships that exist between glutamate/glutamatergic system and the development of neuropsychiatric disorders such as depression have continued to be examined[22,24,51].

Several studies have linked dysregulation of glutamate neurotransmission with the development and progression of neurodevelopmental, neurodegenerative and psychiatric disorders such as autism, epilepsy and schizophrenia[52,53]. There is also emerging evidence (Table 2) linking the pathogenesis of depression to alterations in glutamate and glutamate signalling[12,52]. Levine *et al*[54], using a proton magnetic resonance spectroscopy (MRS) technique examined the relationship between cerebrospinal fluid (CSF) metabolites, such as glutamate and glutamine on depressive symptoms in hospitalized persons with severe unmedicated depression, and reported that compared to control subjects, glutamine level in the CSF of depressed patients was elevated. Also, using high performance liquid chromatography with fluorometric detection, Mitani *et al*[55] examined the relationship between plasma levels of glutamate on severity of depression and concluded that plasma levels of glutamate as well as alanine and L-serine were reflective of the severity of depression. The impact of brain glutamate levels on depression and depression phenotypes have been studied extensively[56-60]. Auer *et al*[56] and Hasler

Table 2 Endogenous glutamate and depression

Subject	Method	Outcome	Ref.
Human	Using a proton magnetic resonance spectroscopy technique	Compared to control subjects, glutamine levels in the cerebrospinal fluid of the depressed patients were elevated	Levine <i>et al</i> [54]
Human	High performance liquid chromatography with fluorometric detection	Plasma levels of glutamate as well as alanine and L-serine were reflective of the severity of depression	Mitani <i>et al</i> [55]
Human	Single voxel (1)H-Magnetic resonance spectroscopy in 19 patients with major depressive episodes	A significant decrease was observed in the levels of glutamate and glutamine in the anterior cingulate	Auer <i>et al</i> [56]
Human	Magnetic resonance spectroscopy	Depressed patients had reduced glutamine and glutamate levels in the dorsomedial/dorsal anterolateral prefrontal cortex	Hasler <i>et al</i> [57]
Human	Magnetic resonance spectroscopy	Compared with controls, depressed patients showed an increase in glutamine levels	Godlewska <i>et al</i> [59]
Human	Meta-analysis	Decreased levels of glutamatergic metabolites were observed in the medial frontal cortex of depressed subjects	Moriguchi <i>et al</i> [60]
Human	Meta-analysis	Glutamate and glutamine concentrations were found to be lower in the anterior cingulate cortex in patients compared to controls	Luykx <i>et al</i> [58]
Human	Functional magnetic resonance imaging and magnetic resonance spectroscopy	Patients with anhedonic major depression showed decreased glutamine but normal glutamate and gamma-aminobutyric acid concentrations	Walter <i>et al</i> [61]
Human	Resting state functional magnetic resonance imaging	Decreased amplitude of low frequency fluctuation level in right putamen and right middle temporal cortex correlated positively with glutamate concentration in female patients with depression	Zhang <i>et al</i> [66]
Mice	Preclinical study	Blockade of glutamate transporter-1 in the central amygdala and prefrontal cortex induced both anhedonia and anxiety	John <i>et al</i> [62, 63]

et al[57] using MRS reported region-specific changes in the levels of brain glutamate in patients with depression. The result of a recent meta-analysis of MRS studies also supported the hypothesis that glutamatergic neurotransmission was involved in the pathophysiology of depression[60]. In another meta-analysis, Luykx *et al*[58] also reported region and state specific alterations in glutamate and glutamine concentrations in depression. The importance of glutamatergic neurotransmission in depression has been further supported by studies that showed altered glutamine concentrations despite normal glutamate levels[59,61].

Abnormalities of the glutamatergic system such as those associated with glutamate clearance at the synaptic cleft and glutamate-related alterations in astrocytic energy modulation have also been observed in depression[61,62]. The results of preclinical studies have also demonstrated that blockade of astrocytic glutamate uptake in the prefrontal cortex and central nucleus of the amygdala was associated with the development of anhedonia and anxiety[62,63]. Furthermore, results from post-mortem and magnetic resonance imaging studies have also revealed the presence of altered expression of glutamate-related genes, elevated levels of glutamate, reduced glutamine/glutamate ratio, and/or reduced levels of glutathione (a reservoir of neuronal glutamate) in brain regions such as the medial prefrontal cortex (which have been linked to depression symptomatology) in persons with depression[64-67].

Finally, the rapid antidepressant effects of drugs such as tianeptine and NMDA receptor antagonist ketamine further validate the importance of glutamate and the glutamatergic transmission in depression [22,68,69]. While reports provide some evidence for the involvement of endogenous glutamate in the pathogenesis and treatment of depression[22,50,69,70], the complexity of the disorder would suggest that the dysregulation of glutamate needs to occur in multiple sites (Figure 1) such as the gastrointestinal tract and brain, as can be seen if there is a communication link involving exogenous glutamate, the gut, endogenous glutamate, and then the brain in a multidirectional pathway which we would call the "GLUTAMATE-GUT-GLUTAMATE-BRAIN AXIS".

The gut-brain axis and glutamate

The impact of the gut (microbiota and gut peptides) in times past was not considered significant in brain development and functioning. Previously, it was believed that the commensal bacteria and their genes which constitute the gut microbiome enjoy a symbiotic relationship with man. In this relationship, they reside in a nutritionally enriched and protected habitat of the human gastrointestinal tract, while they in turn protect humans against colonization of the gut by pathogenic bacteria and provide the body with a rich source of indigestible nutrients. In the light of new evidence, it is now clear that they also play a key role in the brain, either in health or disease.

The gut-brain axis or microbiome-gut-brain axis describes the bidirectional, at times multidimensional system of communication that links the gastrointestinal tract with the central nervous system. It ensures that not only does the central nervous system modulate gastrointestinal function; the gut can

also regulate or modulate brain signalling and impact brain structure and function[19]. There is now ample evidence supporting the view that the microbiome-gut-brain axis can influence the development or progression of central nervous system disorders. Some of these include observations of psychiatric co-morbidities occurring in several enteric neuropathies such as chronic inflammatory intestinal disorders[38,71,72]. The presence of altered gut microbial flora and concentration in neurodevelopmental disorders such as autism[73,74] as well as the results of microbial challenge using pathogenic bacteria or pharmacological manipulations with pre or probiotics, are also pointers to the possible roles played by the gut microbiota in the development of brain disorders[72,75]. Further reports have also shown that the gut microbiota influences brain function *via* its ability to modulate endocrine, immunologic and neurocrine signalling pathways; and brain neurotransmitters[38,76].

Also, several possible mechanisms through which microbiome-gut-brain communication could impact the genesis or progression of central nervous system disorders have been proposed. There have been suggestions that communications occur through the activation of neurotransmitters such as serotonin, dopamine, GABA and noradrenaline in the enteric nervous system; these neurotransmitters are secreted by gut microbiota and are akin to the neurotransmitters in the central nervous system[76]. The possible role of gut peptides and metabolites as mediators of the gut-brain crosstalk have also been suggested[77].

Gut-brain axis and depression

Studies have continued to demonstrate the deleterious effects that alterations in gut microbiome composition and microbiome-related metabolites could exert on the development of obesity, autoimmune disorders, inflammatory bowel disease, irritable bowel syndrome, and neuropsychiatric disorders[77-80]. Also, scientific information showing how gut microbes and gut stimuli (such as intragastric infusion of glucose or fatty acid) can directly influence emotional and cognitive functions [81,82] are pointers to the possible involvement of the gut-brain axis in psychiatric disorders. Several preclinical studies have also shown that the gut microbiota modulates brain behaviours such as behavioural despair, anhedonia and anxiety-like behaviours that have construct validity with clinical depression and anxiety[83-86]. Arentsen *et al*[84] and Kamimura *et al*[86] showed that compared to specific pathogen-free (SPF) mice, germ-free (GF) mice showed impaired social interactions choosing to spend more time with an object than conventionally raised mice. Huo *et al*[85] also observed that the exposure of GF mice and SPF mice to chronic restraint stress paradigm was associated with an increase in open field exploration time in GF compared to the SPF mice; with SPF mice exhibiting more anxiety-like behaviours compared to GF mice. Chronic prebiotic administration has also been shown to exhibit anxiolytic and antidepressant behaviours in mice. The ability of the prebiotic to modulate behaviour correlated positively with its effects on hippocampal and hypothalamic gene expression and its ability to ensure a balance in the concentrations of short-chain fatty acids[87].

Although the mechanisms by which the gut microbiota influences mood and mood-related behaviours are still being studied; there have been suggestions that because the gut and brain share peptide and receptor similarities the gut microbiome is able to modulate brain function through the activity of gut peptides[77]. Also, studies evaluating the impact of gut microbiome modulation (using prebiotics and probiotics) on brain function have demonstrated that chronic treatment with prebiotic had both antidepressant and anxiolytic effects, which could be linked to reduction in stress-induced corticosterone and proinflammatory cytokine release, and modification of the expression of specific genes in the hippocampus[86,87]. Also, probiotics such as GABA-producing *Lactococcus lactis* strain have been shown to possess the capacity to modulate behaviours. In one study, in which *Lactococcus lactis* was grown in both glutamate and non-glutamate supplemented media, a significant increase in GABA production was observed in the glutamate supplemented medium[87], reinforcing the importance of glutamate in the modulation of mood and mood disorders.

There is now ample evidence suggesting that microbes play the role of signalling components in the gut-brain axis. This emerging concept of a microbiota-gut-brain axis suggests that our ability to modulate the gut microbiota may be a potential tool towards the development of novel therapies for complex brain disorders such as psychiatric disorders[19,71,72] (Table 3).

Is there a dietary glutamate-gut-endogenous glutamate-brain axis and how can it impact depression pathogenesis?

Glutamate is a multifunctional amino acid that is involved in intermediary metabolism in the gastrointestinal tract and is also crucial for the normal functioning and development of the brain. In the gut, it is derived from exogenous sources including dietary proteins and from free glutamate present in food additives; also, a fraction of the free glutamate in the lumen is from bacterial synthesis[88]. In the central and enteric nervous systems, respectively, glutamate is the major excitatory neurotransmitter[50, 89].

Glutamate and the glutamatergic pathways are also crucial to microbiota-gut-brain communication. There is increasing evidence that glutamate is both a neurotransmitter and neuromodulator of several functions[77,89]. Glutamate receptors and their transduction molecules have been demonstrated on the epithelial cells of the gut, splanchnic, vagal, and/or pelvic afferents[89-91]. The stimulation of gut

Table 3 Gut brain axis and depression

Subject	Outcome	Ref.
Germ-free mice	Germ-free (GF) mice showed impaired social interactions, anxiety and derangement of brain-derived neurotrophic factor levels	Crumevolle-Arias <i>et al</i> [83], Huo <i>et al</i> [85], and Kamimura <i>et al</i> [86]
GF and SPF mice	Exposure of GF mice and specific pathogen-free (SPF) mice to chronic restraint stress paradigm revealed an increase in open field exploration time in GF compared to SPF mice. Also, SPF mice exhibited more anxiety-like behavior than GF mice under the same external stress	Arentsen <i>et al</i> [84]
C57BL/6J male mice	Chronic administration of prebiotic (fructo-oligosaccharides and galacto-oligosaccharides) have been associated with antidepressant and anxiolytic effects	Kamimura <i>et al</i> [86]
Glutamate and non-glutamate supplemented media	Gamma amino-butyric acid (GABA)-producing <i>Lactococcus lactis</i> strain increased GABA production in the glutamate supplemented medium	Burokas <i>et al</i> [87]

glutamate receptors by dietary or luminal glutamate has been associated with the activation of vagal afferents which directly or indirectly influence brain areas such as the cerebral cortex, limbic system, hypothalamus and basal ganglia[90,92]. Also, the activation of glutamate receptors present on splanchnic, vagal, and/or pelvic afferents, allows the communication of sensory inputs to regions of the brain involved in the gut-brain axis, while, also influencing efferent pathways that convey excitatory or inhibitory inputs to the gastrointestinal tract[89,91].

While in health, the enteric ganglia and the brain are impermeable to dietary or luminal glutamate; there have been reports suggesting that glutamate permeability in these systems increases in diseased states such as enteric neuropathies, or conditions that alter the integrity of the blood-brain-barrier. The gut microbiome also influences brain glutamate, with the results of metabolomic studies revealing that alterations in the composition of the gut saprophytic microflora also affected brain concentrations of glutamate[93,94]. Although there is enough scientific evidence in support of the impact of central glutamate and the glutamatergic system in depression, there is however a dearth of information regarding the possible ways luminal glutamate (either from dietary sources or microbial activities) may influence depression pathophysiology.

However, from the foregoing, it is evident that while exogenous glutamate (from dietary sources or secreted by gut microbiota) can influence brain function through activation of the gut glutamatergic pathways, endogenous glutamate can be influenced by gut microbial composition or metabolites to impact brain function. This shows that glutamate may be more important in the bidirectional communication system of the microbiome-gut-brain axis than previously considered.

GLUTAMATE AND DEPRESSION MANAGEMENT

In the preceding sections, the possible crucial roles that glutamate and glutamatergic neurotransmission play in the pathogenesis of mood disorders were discussed. The results of studies demonstrating the impact of glutamate dyshomeostasis and an imbalance between glutamatergic neurotransmission and synaptic plasticity on mood disorders have been pivotal in the search for novel pharmacotherapeutic strategies[51]. Also, evidence from studies demonstrating the possible antidepressant-like effects of agents acting at the glutamate receptors including NMDA receptors, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and metabotropic glutamate (mGlu) receptors are all pointers to the possible roles of glutamate and glutamate receptors in depression management.

GLUTAMATE-BASED THERAPIES IN DEPRESSION

For more than six decades, drugs that modulate biogenic amines, increasing their availability at the synaptic cleft by selectively blocking the uptake of serotonin and/or norepinephrine have been used in the management of depression. While the safety profile of the newer biogenic amine drugs has improved considerably (compared to the older monoamine oxidase inhibitors and tricyclic antidepressants), they do not address the major drawbacks that have been associated with this mechanism[95-97].

Delayed therapeutic onset, low remission rates, and increased treatment refractoriness are among the major limitations or drawbacks of the standard pharmacological agents for depression treatment[95,96]. Again, up to a third of patients are diagnosed with the treatment-resistant phenotype, adding significantly to the global burden of depression[98]. These limitations are evidence of therapeutics that were still based on an incomplete understanding of disease pathogenesis.

Evidence of ketamine's quick and relatively sustained antidepressant, anti-suicidal, and anti-anhedonic effects in treatment-resistant depression has been documented; and it represents a turning point in our understanding of the possibly crucial role that the glutamatergic system plays in depression. Such findings also prompted further research into developing novel glutamate-based therapeutic targets with better antidepressant effects and without dissociative side-effects, meaning an improvement over ketamine. The results of animal studies evaluating immobility in the forced swim test and tail suspension tests highlighted that both competitive and non-competitive NMDA receptor antagonists had antidepressant-like effects[15]. Decades later, these findings eventually culminated in the approval of esketamine (Spravato®) by the US Food and Drug Administration[99] and the European Medicines Agency[100]; esketamine was selectively approved for use (in addition to a known antidepressant) in adults with treatment-resistant MDD. Apart from this, clinical investigations also continue to affirm that a single intravenous bolus administration of ketamine can evoke a rapid (within 2 h) and lasting (up to 7 d) antidepressant action[101-103].

NMDA antagonists

Ketamine: In humans, ketamine's ability to alleviate depressive symptoms (Table 4) was first highlighted by a small, randomized, double-blind study demonstrating that a single subanaesthetic (0.5 mg/kg) dose of ketamine administered intravenously improved depressive symptoms within 72 h in seven persons with treatment resistant MDD[68]. A larger, double-blind, placebo-controlled, crossover study also found that a single ketamine infusion (0.5 mg/kg over 40 min) had a rapid, robust and mildly sustained antidepressant effect (1 wk) in treatment-resistant MDD[104]. Adverse effects that included confusion, euphoria, dizziness, perceptual disturbances, blood pressure elevation and increased libido were self-limiting[104].

Since the first clinical study that demonstrated the antidepressant effects of ketamine, several other studies have continued to examine its efficacy across other depression phenotypes[104,105]. Diazgranados *et al*[105] demonstrated the rapid anti-depressant effects of a single ketamine infusion in persons with treatment-resistant bipolar depression, which was replicated in a double-blind, randomized, crossover, placebo-controlled study[104]. The impact of ketamine on reducing suicides has also been examined. Ketamine was reported to have a rapid and significant anti-suicidal effect in persons with MDD[101]. While the discovery of ketamine's antidepressant effect was met with enthusiasm, its associated sedative and psychotomimetic effects remain limitations to its use. Therefore, efforts continue to be directed towards blunting these effects. Studies have tried to research the effects of augmenting ketamine with other drugs that are probably better-tolerated; these drugs such as riluzole and lamotrigine have been examined for their ability to either improve ketamine antidepressant effects and/or reduce its psychotomimetic effects[106-108]. However, a number of these studies reported that these add-ons showed no significant ability to improve the course of the antidepressant response (compared to ketamine alone) or reduce the side effects of ketamine[107,108]. Anand *et al*[106] on the other hand reported lamotrigine's ability to decrease the perceptual abnormalities induced by ketamine.

Memantine and amantadine: The dampening of the enthusiasm that arose from the rapid and robust antidepressant effects of ketamine due its psychotomimetic side-effects prompted research into the possible antidepressant activities of other non-competitive NMDA receptor antagonists such as memantine, which has been reported to be devoid of these effects, at least at therapeutic doses[109-111]. The anti-depressant effects of memantine, a low-affinity, non-competitive, open-channel NMDA receptor antagonist which is approved for use in the management of Alzheimer's disease has been extensively studied [104,112]. The results of a preclinical study by Kos and Popik[111] revealed a dose-dependent antidepressant-like response in the tail-suspension test, with the response observed at a dose of 15 mg/kg persisting with sub-chronic administration. However, the results of clinical studies have shown mixed results[110,111]. In one double-blind, placebo-controlled trial in which memantine was administered at doses of between 5-20 mg/d, no significant effects were observed[113]. This result was also supported by another double-blind placebo-controlled study that examined the effect of memantine administered at 10 mg/kg on late-onset depression[113]. However, the result of a large double-blind randomized Finnish study reported a significant antidepressant effect with memantine in persons with co-morbid alcohol dependence[114].

Amantadine is another NMDA receptor antagonist with possible influence on the serotonergic, dopaminergic and monoamine-oxidase systems. The antidepressant effects of amantadine have been observed in situations where it is administered in combination with standard antidepressants such as fluoxetine and imipramine[115,116]. However, clinical trials are limited, mostly using amantadine as an augmentation agent (up to 300 mg/daily) in treatment resistant MDD, where it had shown some modest effects[117].

Subtype-selective NMDA (NR2B) receptor blockers: Investigations into subtype-selective blockers of the NMDA receptor (Table 4) have also been undertaken to by-pass the psychotomimetic effects of ketamine. Along this line, agents such as Ro 25-6981 that can block NR2B receptors have been studied. In preclinical experiments, the NR2B antagonist Ro 25-6981 exhibited behavioural antidepressant-like effects in the forced swim test[118]. The NR2B-selective NMDA antagonist (CP-101,606) that was well-

Table 4 Glutamate-based therapies in depression

Study	Receptor type	Outcome	Ref.
Randomized, double-blind study	NMDAR antagonist	A single subanaesthetic (0.5 mg/kg) dose of ketamine administered intravenously improved depressive symptoms within 72 h in seven persons with treatment resistant major depressive disorder (MDD)	Berman <i>et al</i> [68]
Double-blind, placebo-controlled, crossover study	NMDAR antagonist	A single ketamine infusion (0.5 mg/kg over 40 min) had a rapid, robust and mildly sustained antidepressant effect (1 wk) in treatment resistant MDD	Zarate <i>et al</i> [104]
Open label study	NMDAR antagonist	Rapid anti-depressant effects of a single ketamine infusion in persons with treatment-resistant bipolar depression	DiazGranados <i>et al</i> [105]
Preclinical	NMDAR antagonist	Memantine exhibited a dose-dependent antidepressant-like response in the tail-suspension test, with the response observed at a dose of 15 mg/kg persisting with sub-chronic administration	Kitanaka <i>et al</i> [112]
Double-blind placebo controlled	NMDAR antagonist	Memantine administered at doses of between 5-20 mg/d, showed no significant effects on depression phenotypes	Parsons <i>et al</i> [110], Kos and Popik[111], and Muhonen <i>et al</i> [114]
Preclinical	NMDAR antagonist	The antidepressant effects of amantadine have been observed in situations where it is administered in combination with standard antidepressants such as fluoxetine and imipramine	Czarnecka <i>et al</i> [115] and Maj and Rogóz[116]
Preclinical	NMDA (NR2B) receptor blockers	Ro 25-6981 exhibited behavioural antidepressant-like effects in the forced swim test	Mathews <i>et al</i> [118] and Refsgaard <i>et al</i> [119]
Preclinical	NR2B-selective NMDA antagonist	CP-101,606 that was well-tolerated and devoid of psychotropic side effects was also used in a clinical trial involving subjects with traumatic brain injury	Refsgaard <i>et al</i> [119]
Randomized, placebo-controlled, double-blind study	NR2B-selective NMDA antagonist	CP-101,606 demonstrated efficacy in treatment-refractory MDD subjects	Merchant <i>et al</i> [120]
Cross-over pilot study	NR2B-selective NMDA antagonist	Oral formulation of MK-0657 in persons with treatment-resistant MDD showed a significant antidepressant effect compared with placebo while no improvement in symptoms was noted using the primary efficacy measure	Preskorn <i>et al</i> [121]
Preclinical	AMPA-antagonist	LY392098 and LY451616 exhibited antidepressant effects in a number of animal models of depression; including the inescapable stressors, learned-helplessness models, and exposure to chronic mild stress models	Li <i>et al</i> [122] and Lauterborn <i>et al</i> [123]
Preclinical	mGLu	LY341495, MSG0039, and MPEP exhibited significant antidepressant effects in rodent models of behavioural despair	Jaso <i>et al</i> [7] and Chaki <i>et al</i> [130]

NMDA: N-methyl-D-aspartate; NMDAR: N-methyl-D-aspartate receptor; AMPA: α -Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; mGLu: Metabotropic glutamate.

tolerated and devoid of psychotropic side effects was also used in a clinical trial involving subjects with traumatic brain injury[119].

Other selective NMDA NR2B antagonists such as MK-0657 have also been examined. Again, in a randomized, placebo-controlled, double-blind study, the anti-depressant efficacy of CP-101,606 was demonstrated in treatment-refractory MDD subjects[120], while the result of a crossover pilot study that evaluated the potential antidepressant efficacy and tolerability of an oral formulation of MK-0657 in persons with treatment-resistant MDD observed a significant antidepressant effect compared with placebo using recognized secondary efficacy scales; with no improvement noted when symptoms were assessed using the primary efficacy measure[121].

Other glutamate receptors

The AMPA glutamate receptors are main contributors in excitatory neurotransmission, as they mediate the fast, rapidly desensitizing excitation of many synapses. The potential beneficial role of AMPA receptor modulators (Table 4) in the treatment of mood disorders has been highlighted by studies that have shown that AMPA receptor potentiators such as LY392098 and LY451616 possess antidepressant effects in a number of animal models of depression; including the inescapable stressors, learned-helplessness models, and exposure to chronic mild stress models[122]. Also, they do not seem to affect the extracellular concentration of monoamines[122]; yet they enhance the neurotrophic actions of BDNF mRNA and protein in primary neuronal cultures[122,123]. However, of the AMPA receptor positive allosteric modulators being investigated for MDD treatment, ORG-26576 was amongst the most-promising until it failed Phase II trial. Currently, while the potential roles of AMPA receptor modulators in experimental models of depression are still being researched, the world is still waiting for drugs

whose actions are primarily linked to this. Stimulation of the AMPA receptor has also been associated with mediating the antidepressant-like effects of ketamine and group II mGlu receptor antagonist MGS0039[124], with suggestions that increased transmission *via* glutamatergic AMPA receptors possibly provide a common mechanism of antidepressant response[51].

Kainate receptors are now recognized as important mediators of the pre- and postsynaptic actions of glutamate and GABA, through mechanisms that are still being evaluated[125]. The results of some studies have associated genetic variations in certain kainate receptor subtypes with the therapeutic outcome of antidepressant medications like citalopram and venlafaxine[125-127]. While it is generally accepted that kainate receptors have modulatory effects on synaptic transmission, the paucity of selective kainate receptor subtype agonists or antagonists has hampered research into the possible mechanisms through which kainate receptors modulate brain function and/or impact the pathogenesis and treatment of depressive disorders[125].

mGlu receptors have been shown to regulate glutamate's neuronal transmission through the ability to alter neurotransmitter release or modulate the post-synaptic responses to glutamate release. There is enough evidence from studies to support the notion that regulation of glutamatergic neurotransmission through mGlu receptors is associated with the development of mood, leading to suggestions that they could serve as novel targets in depression management[128,129]. Modulation of the mGlu receptor has also been reported to increase neurogenesis and neurotransmitter release that has now been associated with therapeutic response in humans[128]. Several mGlu2, mGlu3 and mGlu5 receptors' (Table 4) negative allosteric modulators (LY341495, MSG0039, MPEP) have been reported to have significant antidepressant effects in rodent models of behavioural despair[7,130]. Also type III mGluRs (4-8) are mostly expressed presynaptically, modulating glutamate release and response; but while a number of preclinical studies have identified possible type III mGluR novel drug targets such as the mGluR7[131, 132], there is a dearth of clinical studies evaluating the possible therapeutic benefits of these type III mGluRs in depression. There have however been reports that a positive allosteric modulator of mGluR7 (AMN082) has antidepressant-like properties in rodent models of behavioural despair[7], that can be linked to its ability to modulate glutamate transmission in the hippocampus[133].

CAN THE RELATIONSHIP BETWEEN GLUTAMATE AND THE GUT-BRAIN AXIS BE OF THERAPEUTIC BENEFIT IN DEPRESSION?

There is ample evidence that dietary and endogenous glutamate (directly or indirectly) influences glutamatergic neurotransmission in the gastrointestinal tract and the brain, respectively. The gut microbiome has been shown to be involved in the synthesis and release of neuroactive molecules, including those involved in the pathogenesis of depression. Alterations in glutamate concentration and glutamatergic neurotransmission have also been linked to the pathophysiology of depressive disorders. Scientific evidence has shown that diet influences the gut microbiota composition and density, and that both diet and gut microbiota influence emotional behaviour and neurological processes[134,135]. By direct evidence and inference, we now know there is a complex interplay involving diet, the gut microbiome and depression. Hence, specific dietary patterns that can help prevent or mitigate mood disorders, possibly *via* shifts in gut microbiota equilibrium can be identified and offered as components of clinical management.

Also, the use of dietary intervention may prove to be attractive and cost-effective as an alternative or adjuvant therapy in the clinical management of depression. However, despite the tantalizing prospect, the directionality and mechanism of the relationship involving diet, the gut microbiome, and depression are still subjects of research. That being said, diets rich in vegetables, fruits, cereals, nuts, seeds, pulses and moderate amounts of dairy, eggs, fish and unsaturated fats have been associated with a lower incidence of depression[136-139], a view not supported by some studies[140,141]. Research has shown that different microbiota profiles may be associated with positive or negative mental health, emphasizing the behavioural impact of the gut microbiome. Also, if we know that behaviour is determined by the brain's neurotransmitter milieu, then the link involving diet, the gut microbiome, neurotransmitters and depression will be easier to appreciate.

Humans with depression have been shown to harbor variations in gut microbiota which tend towards a general pattern of increases in potentially harmful and inflammation promoting bacteria such as *Proteobacteria*, and a decrease in commensal bacteria, which are normally more abundant[77,141-144]. However, the lack of a specific depression-associated gut microbiota profile is a major challenge[9]. Despite this, the presence of bacteria that produce neuroactive molecules strengthens the link between gut microbiota and behavioural disorders such as depression. *In vitro* and *in vivo* studies have demonstrated the ability of intestinally cultured strains of *Lactobacillus brevis* and *Bifidobacterium dentium* to efficiently produce GABA from monosodium glutamate enriched medium or monosodium glutamate supplemented food, respectively[145,146]; leading to suggestions that this could represent a promising therapeutic approach for depression management. Also, *Lactobacillus rhamnosus* (JB-1) has been shown to reduce stress-induced corticosterone levels in mice and ameliorate depression-like behaviour in the forced swim test; while also increasing brain glutamate and glutamatergic activity[9]. Other specific

relationships involving glutamate are still being investigated, and their direct implications for therapy are being considered.

CONCLUSION

The limitations of the amine theory redirected the research focus to what was supposedly missing in the scientific understanding of the aetiology, course and management of depression. The discovery of the antidepressant effect of ketamine brought attention to the impact that manipulation of the glutamatergic system can have on the management of depression. Also, the role of diet and the gut microbiome in glutamate homeostasis is being continuously examined. As it becomes evident that gut microbes are involved in the synthesis and secretion of molecules that directly impact the brain, including glutamate, we now know that their manipulation through diet can become a cornerstone for the prevention and management of behavioural disorders. However, while glutamate-based therapies for depression are still in their infancy (and much more is dietary manipulation of glutamate balance *via* the gut microbes), it appears that understanding the diet, gut microbiome, gut-brain axis and glutamate link may be the next frontier in advancing our understanding of depression.

FOOTNOTES

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